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AN INTRODUCTION TO MEDICAL PHYSIOLOGY

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FOREWORD

I have known Dr. M. Subrahmanyam for twentyfive years. He belongs to the category of medical teachers who firmly believe in not stuffing the students with unnecessary details but offer sufficient information in a palatable form for easy understanding and quick grasp. He has during the years given clear evidence that students need to be oriented to learn through practicals rather than by merely memorising facts. In this regard the author, in the preface, has made it clear that this book is meant to present to the medical student, principles and fundamentals of functions of cells, tissues and organs without burdening the student with hypotheses, theories, historical background and experimental details. Prof. Subrahmanyam has made a new approach in the presentation of physiology in the right direction. The book covers the ground completely. He has justifiably omitted biochemistry which in recent years has become a vastly grown speciality and the author naturally could not include information pertaining to this field in this book.

Credit needs to be given to the author in having departed from the conventional method of naming the topics by styling them from the viewpoint of function. This is amply illustrated by such titles as respiration, contractile tissue, digestion, reproduction, etc. instead of physiology of respiratory system, gastrointestinal tract and reproductive organs, respectively. This would impress on the student the functional aspect of the cell at its molecular, tissue, organ or system levels.

Each chapter excels the other in its content, simple style and minimum required ink line illustrations. The presentation leans greatly towards clinical applications. This is bound to interest the student. There is nothing redundant in the book and the value of the book is enhanced, as physiological principles in health and disease find adequate coverage. The applied

aspects of physiology enrich the text. This reveals the rich and long experience of the author as a teacher. He has impressed the interdisciplinary nature of the subject and the great role the basic science departments could play in the applications of the physiological principles to clinical situations. Thus, the growing branch of clinical physiology today is brought home to the student. Naturally, the approach of this book differs greatly from the standard text books on physiology.

The book will be of immense value and utility not only to the medical student during his basic sciences course, but also during the clinical years of study. The book will also be useful to those pursuing postgraduate studies in medicine as well as teachers, for quick reference. This book will be popular among medical and dental students should go through the second edition soon. It should then be possible to add illustrations and for the descriptive matter of the illustrations to be put in larger type, to lessen the strain for the reader. A list of references may also be included for the benefit of the talented student.

I wish to congratulate the author for making available this valuable book for the use of medical students. The publishers could take justifiable credit for doing a fine job.

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PREFACE

I felt the need to write a book on Physiology, as early as 1964 when there were practically no books on the subject written by Indian authors. Such of those that were prescribed for study at that time were written by foreign authors and were designed and planned to meet the requirements of their students. Since then, a few text-books have been published in India under Indian authorship. Even so, I felt that what I proposed to bring out could still be useful in that this book is of a somewhat different pattern from what is usually considered to be a text book wherein there is often a plethora of detail pertaining to the fundamental aspects of Physics and Chemistry in addition to lengthy accounts of experimental work related to Physiological concepts. The pre-clinical course is covered in just a little more than a year, in effect. Since a medical student is expected to become very conversant with a standard body of facts and concepts (valid at least for a few years, before new advances make them obsolete), I felt that a direct or bread and butter approach has become very necessary in order that the student can go to the root of the matter and familiarise himself adequately, with the basic aspects of Physiology necessary for the understanding of Medicine. Consequently, a didactic and a somewhat dogmatic presentation has become inescapable. A variety of sources like text-books, reviews, monographs and journals, have been drawn upon in the preparation of the textual material. Biochemistry has been deliberately left out of the purview of this book for the reason, I feel that to write meaningfully and purposefully on Biochemistry, one should be actively engaged in teaching the subject. Further, recently, a few works dealing with Biochemistry have been released in this country and therefore, a section on it in this book will be redundant.

The figures included in this book represent only a selection from a large number, invariably found in textbooks of Physiology. As histology has become a province of the Anatomy Departments in most institutions in this country, figures depicting the structure of many tissues and organs have been omitted. Only those figures which, in my opinion, are very essential for the understanding of the text, have been chosen.

I am much beholden to Dr. D. Jaganatha Reddy, M.D., F. A. M. S., M. R. C. PATH., Vice-Chancellor, Sri Venkateswara University, Tirupathi for graciously writing the foreword to this book.

I wish to express my gratitude to the following staff members of the Physiology Department (past and present) of the Thanjavur Medical College, for their help in the preparation of the manuscript.

Dr. Mrs. G. Sivakumari, Mr. K. Govindadas, Dr. K. Babu John, Mr. Thiagaraj Jacob, Dr. S. Vasantha, Dr. V. Madhini, Mr. Md. Rahamatullah.

Mr. Govindadas rendered great assistance to me in verifying the text by diligently referring to numerous original sources. Dr. V. Kandasamy, Mr. R. R. Bagavathy Raj and Mr. Thiagaraj Jacob helped me in choosing the figures and by reading the manuscript, furnished the feedback for improvement of the original draft.

I am grateful to Dr. (Mrs). G. Sulochana, Reader in Biochemistry, Thanjavur Medical College, for contributing the section on the Renal regulation of acid-base balance. Dr. (Mrs) S. Vasantha, formerly of the Physiology Department and at present in the Department of obsterics and Gynaecology, and Dr. Nalini, Reader in Obstertrics and Gynaecology, helped me in the preparation of the section on Reproductive Physiology. I must make a special mention of Dr. G. Krishnamoorthy, Associate Professor of Physiology, Madras Medical College, Madras, who very kindly perused some parts of the manuscript and suggested improvements in the mode of presentation of the text which have been incorporated. I am grateful to Mr. S. Deva-prasada Rao, artist in the Physiology Department, for drawing most of the figures. The immense task of typing the entire material was very cheerfully carried out by my wife, in spite of her many routine and time-consuming and never ending domestic chores and it is not possible for me to fully acknowledge my indebtedness to her.

I wish to place on record the abundant good will and encouragement I received from Sri R. K. Murti, Managing Director,

Current Technical Literature Co., Private Ltd, Bombay, who was responsible for sowing the idea of writing a book in my mind, way back in 1962.

I owe not a little to Sri T. S. Krishna Rao, of the M.K. Press, Thanjavur, who undertook the printing of this book for making available to me his expertise and long experience in his field.

To conclude, I earnestly hope that this work of mine will be of use to those for whom it is meant. Any comments and suggestions from fellow teachers of Physiology and colleagues in other disciplines in Medicine, will be thankfully received and adopted for future use.

May, 1974

The Author

ACKNOWLEDGMENTS

I wish to express my gratitude to the several authors and publishers in addition to those to whom credit has been given after the legends for some of the figures in this work. I am deeply obliged to them for the courtesy shown to me by them and the readiness with which they accorded permission to me to use figures (referred to below) in their publications.

Green, J. H., *An Introduction to Human Physiology*, Oxford University Press, London, 1963 (Fig. 133 p. 112)

Houssay, B. A., *Human Physiology*, McGraw-Hill Book Company, New York, Second Edition, 1955 (Fig. 141, p. 266)

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I should also like to acknowledge that the figures (mentioned within brackets) that appeared in the following publications were utilised by me. I am indebted to the authors and publishers.

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Davson, H. & Eggleton, M. G., Principles of Human Physiology, J. & A. Churchill Ltd., London, 13th edn., 1962. (Fig. V-29, p. 835 ; Fig. 1156, p. 144 ; Fig. 11207, p. 355).

Harris, Gilding & Smart, Experimental Physiology, J. & A. Churchill Ltd., 6th edn., 1956. (Fig. 14, 16, p. 191)

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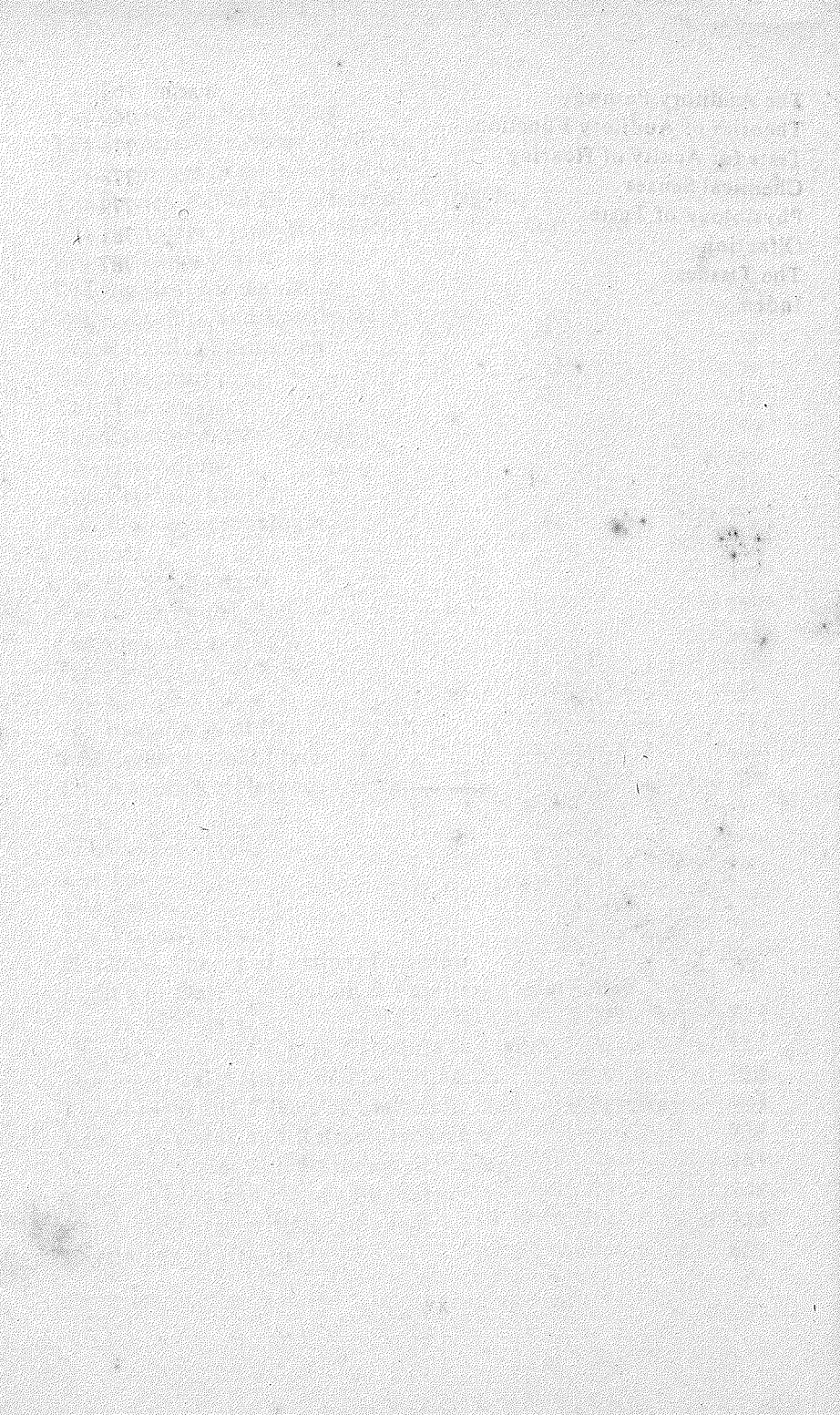
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THE CELL

THE human body is made up of myriads of cells kept in proper positions in relation to each other by intercellular cementing substance. Each cell enjoys a limited biochemical autonomy. The human body cells, of course, cannot live independently of each other though they have the same cellular internal structure as the unicellular creatures, like the amœba. During the course of evolution, the human cells lost such a faculty. They are all bathed in the extracellular fluid with which they have interchanges as regards, water, electrolytes and organic substances of a wide variety. It is a truism to say that the cells in the body are interdependent. Each cell, by its physiological and biochemical actions, makes it possible for the other cells not only to exist in a vegetative manner, but also to discharge their respective physiological functions. It is not necessary at this stage, even to give examples in support of this statement. The reader, as he becomes more and more familiar with the facts of Physiology, will realise the truth of such a statement. The actual functioning of the biochemical machinery of the individual cell falls outside the scope of Physiology. In this section, it is proposed to introduce a few structural features of a typical cell. The individual peculiarities of different kinds of cells forming the various tissues in the body, will be referred to, in the relevant sections.

A typical cell in the human body (as in other animals)—has a cell membrane separating it from other cells in its neighbourhood. The plasma membrane (100 Å thick) is the functional boundary of the cell. It is highly discriminatory as regards the materials it permits to be transferred across it. In general, under the influence of purely physico-chemical forces, it allows the free passage of water and certain anions as well as some organic substances of low molecular weight, like amino acids and glucose. This membrane is apparently impermeable to cations like Na^+ , K^+ and also to proteins and substances of high molecular weight. There seems to be a built-in mechanism for extruding

sodium ions from inside the cells and at the same time to keep potassium ions within the cell boundary. Till recently, it was not possible to see this membrane except as a line around the cell even with the use of a microscope. The electron microscope which is relatively a very late-comer as an aid in biological investigations, has revealed some kind of boundary around the cell. From other studies, it has been deduced that there is a double layer of lipid molecules which are arranged in the manner of a palisade. In each layer, the molecules are disposed with their long axes perpendicular to the cell surface. A layer of carbohydrate molecules is adsorbed on the external aspect and a layer of protein molecules just inside the inner layer of lipid molecules. The plasma membrane, however, may not be a thin structure; it may be in the form of an actual zone or cortex enclosing the cell completely.

The cytoplasm or cell matter is a jelly-like substance made up of protein and water. The outer portion of the cytoplasm is known as ectoplasm and is much clearer and less granular than the endoplasm inside. There are many structures known as inclusions in the cytoplasm and they are described below. There is also a fine reticulum which may be formed of interwoven membranes. These may provide a communication between the innermost parts of the cell and the exterior, for the transfer of substances. Those inclusions with a definite structure, are known as organelles. These are :— 1) mitochondria, and 2) microsomes. The former are yellowish particles of different shapes. Their ultra-structure has recently been revealed by the electron microscope. They contain enzymes which are concerned with the cell oxidative processes. The microsomes are smaller particles and their function is not known. The cytoplasm also contains fat droplets and glycogen granules which are used by the cell for obtaining energy. The centrosome is a small structure which becomes active during cell division. It is pertinent to mention that the nerve cell has no centrosome and hence is incapable of reproducing itself. The centrosome is found near the nucleus of the cell. The Golgi apparatus is a network of fibrils, probably concerned with secretory activity. A few vacuoles or empty spaces are usually found. Pigmentary granules and zymogen

granules may be found in certain cells. Electron microscope studies of the cytoplasm have revealed particulate material known as ribosomes which are intensely basophilic in staining reaction. These contain ribonucleic acid which is concerned with protein synthesis. Ribosomes are found in the nucleus also.

The nucleus, having a different kind of substance or karyoplasm in it, is separated from other cellular constituents by a nuclear membrane. Chromatin material which is deeply staining, is found in the nucleus in the form of distinct strands or chromosomes which are rich in nucleoprotein. These control the metabolism of the cell and also take an active role in cell division. They carry genes which are arranged on them in a definite order and these are responsible for transmitting hereditary characteristics. One or two small round bodies known as nucleoli are found inside the nucleus. They are prominent in growing cells and may influence protein synthesis. They are acidophil in reaction. The nucleus is very necessary and indispensable for the existence as such, of a cell. No cell can continue to live if its nucleus is lost or damaged. The red blood cell or erythrocyte is the only exception among all cells. Though they are devoid of nuclei, they have to be considered as living cells.

TRANSPORT ACROSS CELL MEMBRANES

Substances like ions and organic materials which are needed by the cell for its activity, have to be transferred across the cell membrane. This takes place in two possible ways—passive transport and active transport.

Passive transport: When the movement of a substance is dependent only on purely physicochemical factors like a concentration gradient (different concentrations of a particular substance on the two sides of the membrane—outside and inside), an electrical potential difference between the exterior and interior of the cell, transport is said to occur passively. Such a process holds good in the case of anions like Cl^- , bicarbonate ion and urea. Concentration differences give rise to 'diffusion' of the substance from the side of greater concentration to that of the lesser one.

The movement of water from one side to the other of the cell membrane is subject to osmotic forces arising out of concentration differences of substances incapable of passing through the cell membrane ordinarily.

Active transport: The cell cannot depend entirely on passive transfer of substances for its existence or for carrying out its physiological role. In the case of many substances, an 'active' process, utilising energy derived from biological oxidations in the cell interior, is responsible for taking up substances by the cell from the exterior and for eliminating or 'secreting' products of its own internal activity. The renal tubular cell in the proximal tubule, actively 'reabsorbs' sodium ions from the tubular lumen (see under 'Kidney') and unloads them into the extracellular fluid, to be finally carried away by the blood. Secretory cells of the various glands, exocrine and endocrine, expel their secretions into either ducts or the blood itself respectively, by an active energy-consuming process. Active transport operates against electrochemical gradients, unlike passive transport which is dependent on them and occurs in the direction of such gradients. Hypothetical substances known as carriers are said to convey materials across the cell membrane in active transport. Sometimes, a carrier is thought to transfer one substance in one direction and another in the opposite direction, as in the case of Na^+ and K^+ .

THE BLOOD

THE blood is a very complex fluid made up of cellular or formed elements suspended in the liquid known as plasma which holds a large number and a wide variety of crystalloids and colloids in solution. The blood appears red to the eye, since it absorbs the shorter wavelengths of the solar spectrum. Actually, hæmoglobin, the pigment of the blood cells is pale orange in colour. When aquatic animals, in the distant past, invaded the land and became terrestrial creatures, blood and the extracellular fluid was presumed to be of the same composition as sea water. During the passage of millions of years, sea water has changed as regards its constituents and the present day ocean has a different constitution from that of the extracellular fluid and blood.

The formed or cellular elements constitute about 45% by volume (hæmatocrit) of the blood, red blood cells or erythrocytes accounting for nearly the whole of this. The leucocytes and the platelets occupy very little space and may be entangled in the buffycoat at the top of the packed cell column, after blood has been allowed to stand for an hour or more. Detailed consideration of the cells of the blood is relegated to later pages.

The composition of the plasma is as follows:—

Water—91-92%

Proteins—7-9%

Inorganic constituents—0.9%

Organic constituents—a large number of substances are present in a fairly constant proportion along with hormones and enzymes of variable concentrations.

Details concerning organic substances and the factors which regulate their levels, except in a few instances dealt with in appropriate sections, fall within the domain of biochemistry.

The main inorganic cations of blood plasma, blood and red cells.

	(milligrams per 100cc)			
	Sodium	Potassium	Calcium	Iron
Plasma	340	20	10	negligible
Cells	20	410	nil	100
Whole blood	190	220	5	50

The specific gravity of blood is about 1055-1065, that of plasma being 1030 and the formed elements 1090 (water - 1000).

Functions of blood: 1) It serves as a vehicle for the transport of respiratory gases—oxygen and carbon dioxide. Consideration of this aspect is postponed to the section under Respiration.

2) The blood carries waste products and metabolites produced by the various tissues, to the kidneys and sweat glands for excretion from the body (see under Kidney).

3) The transport of products of digestion, like amino acids, glucose, fatty acids etc. from the alimentary canal to the liver where some of them are processed or converted into suitable forms for utilisation in the body, as well as their redistribution among the cells of the body, is known as the nutritive function of blood.

4) The blood holds a few litres of water which belongs to the extra-cellular compartment of body water. Because of its mobility, it serves to maintain water content of tissues at a normal level and helps in distributing water equitably among the various parts of the body, when the body water increases or decreases.

5) Water has a high specific heat. Hence the blood has a great role to play in the maintenance of body temperature. It 'mops' up the heat produced in the body or gained from the environment or food and thereby minimises the tendency for body temperature to rise. Further, when more blood is diverted

to the skin vessels which dilate on a warm day, heat is lost by radiation to the surroundings. The evaporation of sweat brings about cooling of the body to a great extent because of the high latent heat of vapourisation of water. The physical properties of blood which is basically a watery medium, combined with its mobility from one part of the body to another, makes it an efficient agent in thermostasis.

6) Many hormones and vitamins that find their way into the blood from the ductless glands and the alimentary tract are conveyed to their appropriate destinations in the body where they exert their specific actions. The regulatory activity of these substances is rendered possible by blood flow.

7) The presence of certain protective substances like immune bodies and of white blood cells (leucocytes) enables blood to discharge a protective function against infective micro-organisms.

RED BLOOD CELLS

The term red cell or erythrocyte is a misnomer. In the fresh state, it is seen under the microscope to be a pale orange yellow disc. In bulk, however, blood takes on a red colour. The human erythrocyte is a biconcave circular disc looking like a dumb-bell in the side view. It has been conjectured that this shape of the cell was evolved as a compromise between the sphere in which the maximum volume (of hæmoglobin) has been enclosed for a particular size of the cell and a flat disc which has a large surface area (for transfer of gases) with very little material (hæmoglobin) contained in it. No point within the cell is far away from the surface, because of its shape. An average human red cell has a diameter of about 7 microns (μ or micron – 0.001 mm) in the dry state—a little more in the fresh condition. The thickest portion along the edge measures about 2.5 microns, the surface area is about 120 sq. microns and the volume around 90 cubic microns. It has been estimated that the mean corpuscular (cell) content of hæmoglobin lies between 25.5 and 31.5 micromicrograms ($1/10^{12}$ gm) and hæmoglobin, in hundred cubic centimetres of packed red cells, weighs about thirty five gms.

(MCHC percentage). Red cells can be separated from the plasma by whirling a sample of blood at 1500 revolutions per minute, in a centrifuge for about half an hour. The heavier part, namely the cells, settles at the bottom leaving a clear column of plasma above. The cellular elements (almost wholly of red cells) form 45% of the blood volume and this value is known as the hæmotocrit value of packed cell volume. Red cells occur to the extent of about 5×10^6 cells in a cubic millimetre of blood, men usually having a slightly higher count than women. Physiological increase in the count occurs in muscular exercise (in humans this is not due to splenic contraction) and after staying at high altitudes for some time. Permanent inhabitants of high mountainous regions, as in Alps and Himalayas, have high cell counts. A fall in the cell count is definitely pathological. Polycythemia Vera is a condition arising out of a pathological increase in count, of unknown cause. Mountain dwellers, if they choose to live at lower altitudes, will have a fall in their erythrocyte count, showing that it is accurately adjusted to the availability of oxygen.

Majority of the red cells conform as regards size and other characteristics, as mentioned above. Sometimes a few abnormal forms may be seen even normally. Only if these abnormal forms occur in large numbers, they are to be considered as pathological.

- | | |
|----------------|---|
| Microcyte | — an erythrocyte of diameter less than 7μ |
| Macrocyte | — a large red cell. |
| Megalocyte | — This is a large red cell seen in cases of pernicious anæmia. It is derived from a megaloblast, an abnormal precursor. |
| Polychromasia | — The cell matter takes on dual staining, appearing both basophilic in some parts and eosinophilic (normal reaction due to hæmoglobin) in others. |
| Poikilocytosis | — Occurrence of cells of different shapes. |
| Anisocytosis | — Presence of cells of widely different sizes though of the usual shape. |

- Punctate basophilia** — Particulate material taking dark basic stains sprinkled over the cell matter.
- Cabot's rings** — Threads or rings of basophilic material derived from the nuclear matter, persisting in the circulating red cell.
- Howell-Jolly body** — Fragments of nuclear matter present in some red cells.

When a drop of blood is drawn into a thin uniform smear, the cells separate out, to be seen individually, at least in the tail end of the smear. When a wet film of blood—a drop of blood diluted with 0.9% sodium chloride and a cover slip placed over it—is examined under the microscope, some red cells may be seen to attach themselves to each other to form what is called rouleaux (piles of coin appearance). Spherocytes (red cells which tend to be somewhat spherical and not biconcave) do not form such congregations. Rouleaux formation is also known as pseudo-agglutination. Agglutination is an abnormal clumping and can be seen when mismatched bloods are mixed. In disease conditions, even in a blood smear, clumps may be seen and this is known as sludging.

Erythrocyte sedimentation rate (suspension stability) — When a column of blood, enclosed in a graduated glass tube of narrow inner diameter (an anticoagulant is added to it to keep it in the fluid state), is allowed to stand for an hour or more, the cells which are heavier than the plasma, settle down slowly, leaving a clear layer of plasma above (0.4cc of 3.8% sodium citrate is added to 1.6cc of blood drawn from an arm vein). The height (or depth) of the clear portion (plasma) read after an hour, gives the erythrocyte sedimentation rate (E. S. R.). It is about 1–3mms in a male adult, slightly more in women and children (new born children have low E. S. R.). Physiologically, increase is seen only in women during the destructive phase of the menstrual cycle and in pregnancy. In certain diseases, the ESR shows a great increase. Notable examples are tuberculosis and acute rheumatic fever. Infective conditions like pneumonia and streptococcal infections also bring about an increase. In allergic conditions and spherocytosis (acholuric jaundice), ESR is reduced.

Certain factors influencing ESR: Theoretically, if the disparity in the specific gravities of the plasma and the red cells is great, cells settle down rapidly. But in cases of high ESR, there is no appreciable change in specific gravity of either cells or plasma. While again, lowered viscosity of plasma and increase in the size of the cells individually, can increase the rate of sedimentation, yet they do not seem to be the cause. Clumping of cells as occurs in disease states, seem to increase the rate because the weight of the suspended particles increases without much increase in the surface area. The rise in euglobulin and fibrinogen concentration in plasma, which affects their relative proportion, seems to affect the red cells in some way, causing them to adhere to each other. Blood from patients with tuberculosis or rheumatic fever cannot be spread into thin uniform smears, unlike normal blood. The pathological blood smear has a granular appearance. In addition to the qualitative change in the plasma, other factors also influence the rate. Spherocytosis retards the sedimentation as does a fall in temperature or a rise in the erythrocyte count. Raised temperature accelerates the sedimentation. ESR, though originally held to be of great significance, is considered to be of limited value now. ESR rises whenever there is tissue damage. The increase in ESR is greater in inflammatory conditions than in the case of growths. Malignant growths cause greater rise than benign ones. General infections and localised inflammatory conditions of a severe degree are the commonest causes of raised ESR. In all these, there is an associated increase in fibrinogen and globulin levels of plasma. This should increase the viscosity of blood and logically slow down sedimentation, but actually it hastens sedimentation. Sometimes, even in the absence of a raised body temperature, fast pulse and leucocytosis, ESR may be high and indicates a recrudescence of the disease process. ESR can be used to differentiate between conditions having similar symptomatology like coronary thrombosis and angina pectoris, gonococcal arthritis and osteoarthritis, ovarian cyst and acute appendicitis. Hence, the determination of ESR is a useful diagnostic aid.

Hæmolysis: The presence in the free state (dissolved) of haemoglobin in plasma, imparts a yellowish tinge to the plasma

and in such a condition, haemolysis is said to have taken place. This term indicates destruction of the erythrocytes which sets free haemoglobin into the plasma. It is not strictly necessary for the cell stroma to be destroyed or disorganised, to allow haemoglobin to escape into the plasma. What is left behind after a red cell loses its haemoglobin, is known as a ghost or shadow cell.

Haemolysis is brought about by certain chemical agents (haemolysins) which act in different ways.

1. Acids and alkalis—if red cells are suspended in these, haemolysis occurs. The exact mode of action is not known. Bile salts and saponin also act in an unknown manner.
2. Fat solvents like chloroform, ether and alcohol haemolyse blood by dissolving the lipid elements in the cell membrane and stroma.
3. Haemolytic antibodies can develop in the body of an animal which has been sensitised to red cells of an animal of another species. Haemolysis can occur in Rh group incompatibility—(see under blood groups).
4. Bacterial haemolysins – Organisms like streptococcus haemolyticus and several others, as they multiply in the host animal, produce powerful haemolysins causing haemolysis which is a toxic manifestation of the infection.
5. The venom of certain snakes like the cobra, produce haemolysins by their action on certain plasma constituents. Lecithin in blood is converted by the loss of unsaturated fatty acids into lysolecithin, a haemolytic agent.
6. Erythrocytes can maintain their normal shape and size indefinitely when suspended in a solution of sodium chloride of strength 0.9% which is known as *normal* or *isotonic saline*. This is isosmotic with the interior of a red cell. But all isosmotic solutions are not isotonic as for example, an isosmotic solution of urea the solute in this case being able

to pass into or out of the cell. The red cell can withstand lowering of the concentration of sodium chloride upto 0.45% but over a range of reduction from 0.45% to 0.35% more and more of the cells rupture on account of entry of water into the cell and below the lower limit none will remain intact. For frog's cells the concentration of normal saline would be 0.65%. The term laking of blood refers to lysis of all red cells and staining of the plasma. On the other hand, when cells are immersed in solutions of strength higher than 1%, water is abstracted from the cell which becomes smaller and irregular in outline (crenation). Osmotic resistance of a red cell is indicated by the lowest strength of sodium chloride (in water) in which the cell can maintain its integrity. In acholuric jaundice, the spherocytes are very fragile and hæmolyse even at concentrations above 0.45%. In pernicious anæmia, however, fragility is reduced, the red cell tolerating very low concentrations. Fragility is determined by putting a drop of blood into each of a row of ten Kahn tubes containing salt solutions, which are arranged in the order of increasing strengths from 0.1% to 1.0%. The highest concentration in which the supernatant solution is tinged with red colour gives the index of osmotic resistance of the particular sample of blood.

BLOOD GROUPS AND TRANSFUSION

It is estimated that a human being cannot afford to lose suddenly, by bleeding, more than about a third of his total blood volume. When the blood loss is less, compensatory mechanisms are put into operation to offset the loss. But, when a large fraction of the total quantity of blood is shed, it becomes emergent to restore the blood volume in order that fatal circulatory and other disturbances are prevented. It is in this regard that the discovery of blood groups by Karl Landsteiner and his co-workers (1901 onwards), became an epoch making one to serve as a great life-saving measure. The existence of 4 groups or types of blood among all human beings, irrespective of race and sex, was shown as a result of investigations covering a period of about ten years. Blood transfusion evolved into a precise therapeutic measure in the treatment of hypovolæmia (diminished blood volume).

The four groups of blood – only one of which is found in any one human being – are characterised by the undermentioned features. Some confusion had been caused in the beginning, by the differences in nomenclature of the blood groups, between two early workers, Moss and Jansky. The modern practice is to name the group to which a person belongs, on the basis of the agglutininogen or group specifying substance (arbitrarily named) which is situated on the surface of the red cell. In the plasma, a corresponding agglutinin is found. Blood groups are seen in dogs, as reported recently.

Blood group	Agglutininogen in the corpuscle (group specific substance)	Agglutinin in plasma
A	A	Beta (β) or anti B
B	B	alpha (α) or anti A
AB	A & B	no agglutinin
O	No agglutininogen	alpha and beta ($\alpha\beta$) or anti B & anti A.

The agglutininogens of the RBC are mucopolysaccharides and they are antigenic in nature in that, if the blood of one group is injected (in a small quantity) into a person of another group, or into a laboratory animal such as a rabbit, antibodies (agglutinins) will be produced in the recipient, which are capable of agglutinating or causing the clumping of those red cells. When the cells of one blood group are mixed with the plasma of another group, agglutination of the cells will take place. Only in the case of cells of O group ordinarily, agglutination will not occur when these are mixed with plasma of other groups of blood. Usually, blood transfusions are given in quantities of about half a litre (a pint) or 1 litre (2 pints). If there is incompatibility between the blood transfused (Donor's blood) and the blood of the recipient, the donor's corpuscles are agglutinated by the recipient's agglutinin. Except very rarely, the recipient's cells are not agglutinated by the agglutinins in the donor's blood, since, these get

diluted in the much larger volume of the recipient's blood. The exceptions are the cases in which the donor's plasma has a very high titre (concentration) of agglutinins and this may bring about an agglutination of the recipient's red cells.

'A' group subjects have been later re-classified into A_1 (majority) and A_2 types and hence AB group is also to be considered as A_1 B and A_2 B. Cells of A_1 sub-group have two agglutinogens, A and A_1 , while the A_2 cells have only the A agglutinin. For transfusion purposes, ordinarily, it is not necessary to discriminate between A_1 and A_2 groups. They are to be considered as one (A group). A_1 cells are strongly agglutinated by alpha agglutinins, but not A_2 cells, on which alpha agglutinins do not have a pronounced action. A_2 cells seem to have, in addition to A group specific substance, type O agglutinin, though O group is conventionally described as lacking both A and B agglutinogens. Hence, A_2 cells may sometimes be clumped by an anti-O agglutinin. The statements pertaining to A_1 and A_2 sub-groups apply equally to A_1 B and A_2 B sub-groups also. The A_2 group cells may contain the alpha (reacting with A_1 and A_1 B cells) in addition to Beta agglutinin.

It has to be pointed out that the blood group of a subject is determined at the time of conception, based on the parental groups, according to laws of inheritance of blood groups. The blood group of an individual remains permanent and cannot be changed at all, even by massive replacement transfusion, as it is genetically determined. The agglutinogens are secreted in the saliva of some people.

Inheritance of groups: There are three allelomorphic (alternative) genes, any one of which may be present in each of the chromosomal pair concerned with the transmission of the blood group to the off-spring. Thus a pair of genes, one derived from the spermatozoon and the other from the ovum, will determine the blood group of the foetus. O group gene is recessive while A and B group genes are dominant. Four types of gene combinations are possible, as depicted in the following scheme.

●—Paired genes				Genotype (combination of genes from parents)	Group of offspring
O			O		
or			or		
A	●	●	A	OO	O
or			or	OA or AO	A
B			B	OB or BO	B
	I	II		AB or BA	AB
I—chromosome from one parent				AA	A
II—chromosome from the other parent				BB	B

The following facts emerge from the foregoing description of inheritance.

A child of A group or B group should have inherited the 'A' or 'B' gene respectively, from at least one of its parents. A child of AB group, inherits 'A' gene from one parent and 'B' from the other. So, neither of the parents can be of O group. A child of 'O' group can have both or one of its parents belonging to other groups – i. e. – A, or B. But, if both are of AB group, the child cannot be of O group.

Agglutinins: At birth, while the agglutinogens are already present in the red cells, the corresponding agglutinins are almost absent from the plasma. In a few months after birth, the development of the agglutinin in the plasma appropriate to the agglutininogen in cell, takes place. In A group blood, Beta agglutinin (anti B) is formed while in B group blood, alpha agglutinin (anti A) appears. The maximum concentration or 'titre' is attained at about the tenth year of age and thereafter the concentration declines very gradually with age. It is because of the absence of agglutinins at birth, that a new born baby can be transfused with blood of any group, though even this is sometimes hazardous, as it happens when the baby derives agglutinins from the maternal blood through the placenta. In this case, the mother's agglutinins disappear within ten days after birth. Hence, it may be safer to use mother's blood for transfusion, if there be necessity for that. It is inexplicable how only a particular agglutinin and no other, develops in the blood of each individual.

Typing the group to which a person belongs: Two sera are used—one of group A blood (Beta agglutinin) and the other of group B blood (alpha agglutinin). A drop of each serum is placed on a glazed white porcelain tile, sufficiently apart to preclude their mixing with each other. A small quantity of blood (a few drops) are mixed with a few cubic centimeters of 0.9% saline, to obtain roughly 1 in 10 suspension of cells. A drop of this fluid is added to each of the drops of sera, without contaminating one with the other, on the tile. The tile is gently rocked to mix the cell suspension and the serum thoroughly. After waiting for about ten minutes or so, the tile is examined with the naked eye for the occurrence of agglutination which is indicated by the appearance of small red particles suspended in clear fluid (cayenne red pepper). The particles are the masses of agglutinated red cells. Minor degrees of clumping may not be visible to the eye. It is better to use microscope slides instead of a porcelain tile. The test sera are placed at the ends of the slide. The cell suspension is added to both sera, avoiding contamination of one serum with the other. Cover slips are placed on the drops after mixing the serum with the cell suspension. First, agglutination is looked for in the two samples with the unaided eye. The slide is placed on a clean white paper to provide contrast. Confirmation of the observations is done by examining the slide under a microscope. Even minimal clumping can be easily detected this way. Sometimes, in order to hasten the agglutination, the slide is slightly warmed. The group to which the sample of blood which is tested, belongs, can be found by noting the occurrence of agglutination. The group is assigned with reference to the table as follows:

	A group serum containing Beta agglutinin	B group serum containing alpha agglu- tinin	Group of the unknown cells
+ agglutination	—	+	A
— no agglutination	+	—	B
	—	—	O
	+	+	AB

It is to be noted that B group cells are agglutinated by the serum of A group blood and vice versa. AB group cells are agglutinated by both A and B group sera, whereas O group cells are agglutinated by neither. Most often, O group blood could be transfused to a person of any of the four groups without a risk and subjects of 'O' group were therefore known as universal donors. It is now realised that it is not safe to transfuse O group blood to all. There are some people who react adversely to such transfusions and those subjects of O group whose blood agglutinates the cells of recipients to whom they donate blood with disastrous consequences, are known as dangerous 'O' group people. The agglutination of the recipient's cells seems to be due to a high concentration of anti-A and anti-B agglutinins in the 'O' group blood, which inspite of dilution in the host's blood, can still bring about agglutination of the host's cells. In some cases, the O group blood may contain alpha agglutinin which agglutinates A₁ group cells. Repeated O group transfusions may set up anti-body production in the patient.

In a well organised blood bank, it is possible to type the blood of any person, so as to arrange for him to be given the blood of the same group. But, in view of other possible differences regarding subgroups, between the blood to be given and the blood of the recipient, these are directly matched (cross matching). The cell suspension made from each sample of blood is mixed with the serum of the other to ensure that no agglutination occurs. In a blood bank, the donor's serum is mixed with the recipient's cell suspension to eliminate agglutination of the recipient's cells after transfusion, owing to a high titre of agglutinins in the transfused blood. All this is to make certain that the given blood is exactly of the same type as that of the person requiring a transfusion. Direct or cross-matching is resorted to when anti-sera are not available for typing samples of blood and also as an additional precaution even when the groups are known after typing and it is in this way that subgroup incompatibilities are avoided.

Several workers have discovered certain minor blood groups-like M, N, P etc. These are not independent groups. They are additional agglutinogens occurring along with the standard ones

of A, B, AB and O and are not of importance for purposes of transfusion. They are useful in anthropological or ethnic or sociological studies – in tracing the geneology of families and like purposes.

The Rhesus (Rh) factor: It is a remarkable piece of persistence in a line of enquiry that Landsteiner made a discovery of the Rh factor in 1940, almost forty years after his original one of the classical blood groups. Small quantities of the blood of Rhesus macacus monkey were injected into the rabbit to generate antibodies or agglutinins to the Rhesus cells. Blood from human subjects was tested against the rabbit serum. It was seen that in a white or caucasian population, as in Europe, 85% of all those tested showed the presence of the so-called Rh (after the Rhesus monkey) antigen in their blood and hence they were termed as Rh + Ve and those that lacked this antigen were considered to be Rh negative. In oriental races (mongoloid mostly) and among the negroes, there are almost no Rh – Ve individuals. It is strange that in Europe, among the Basques inhabiting the Pyrenees mountain region between Spain and France, almost all the people are Rh negative. In India, the Rh factor occurs in nearly every one of the population. Unlike in the case of the classical groups, there is no naturally occurring anti-Rh agglutinin in the blood of even Rh negative individuals. Only when a subject is sensitised to the Rh antigen, an anti-Rh agglutinin is produced. The time of generation of anti-Rh agglutinin, after an exposure to the antigen, is about 12 days. But, once an antibody appears in the blood, it persists for the rest of the life and its titre will rise sharply when a second exposure occurs. It is to be emphasized that the Rh agglutigen exists in addition to one of the A, B, O and AB antigens. These are not mutually exclusive.

The Rh factor assumes importance under certain circumstances.

1. When a Rh negative patient (male or female) is transfused with Rh positive blood for the first time, no adverse effects are seen. But, if after anti Rh agglutinins are developed (in about 12 days) it is necessary to transfuse Rh positive blood again, agglutination will occur with harmful effects.

2. In the case of a Rh negative woman with a Rh positive husband, if the first child happens to be Rh positive, in subsequent pregnancies, should the fœtuses also be Rh positive, their survival either during pregnancy or after birth is endangered. Either still birth or neonatal death may occur, due to a condition known as Erythroblastosis Foetalis. These Rh positive babies, if they happen to be born alive, suffer an intense hæmolysis, owing to the maternal antibodies (to Rh antigen) leaking into the fœtal circulation. The rapid destruction of the red cells in large numbers may end in death of the baby. The condition further intensifies in later pregnancies, if the fœtuses are Rh positive. The method of saving these newborn babies, is to perform an exsanguino transfusion with Rh negative blood—gradual removal of all Rh positive cells with concurrent replacement by Rh negative cells belonging to the same main group (A, B, AB, O). It is believed that during the first pregnancy, even though there does not seem to be a direct communication between the maternal and fœtal circulations, a few fœtal Rh positive blood cells may escape into the maternal sinuses, thereby sensitising the mother to the Rh antigen. Sensitisation to the Rh antigen may also take place when the mother has had a transfusion of Rh positive blood either prior to her marriage or before her first pregnancy. Rh positive blood should never be given to an Rh negative person, be it male or female, except as a life-saving measure. The possibility of Erythroblastosis Foetalis occurring even during the first pregnancy should deter one from giving such a transfusion to young girls and unmarried women. Rarely, erythroblastosis fœtalis may occur in respect of A, B, AB and O groups also. Even though, on theoretical grounds, erythroblastosis fœtalis should be met with frequently, yet for unknown reasons, it is not so common. Perhaps the mother's capacity to produce antibodies, in most cases, may not be high.

The Rh agglutinin (a protein) is inherited by a child through a dominant gene. Rh negativity is a recessive characteristic. Even if one parent is Rh positive, the other being Rh negative, the child will have the agglutinin. Rh negative subjects

have both their parents Rh negative. In the beginning, Rh agglutinin seemed to be a single factor. Several variants of Rh agglutinin have been unmasked. The terminology as regards the Rh subgroups, is rather complicated and various workers have assigned different symbols to identify the same factor. To avoid confusion in a very brief treatment of blood groups, as in this chapter, only Fisher's classification is referred to. Six allelomorphous genes C, D, E, c and e (d has not been met with as yet) could give rise to a large number of genotypes (parental combination of genes) like CDE, CDe and so on. The lower case letters c, d and e are the reciprocal factors representing absence respectively of C, D and E antigens. The presence of D agglutinin on the cell makes it Rh positive (in the usual meaning of the term). The other antigens C and E also could be taken to make the blood Rh positive, but these are not strongly antigenic because they do not evoke the formation of antibodies (agglutinins) in high titres. Subjects possessing Rh antigens other than D, while acting as donors are to be taken as Rh positive, yet when they have to receive blood, may be considered as Rh negative. A truly Rh negative person is one represented by the genotype cde. It is rather difficult to detect the Rh antigen. A specially prepared serum containing anti-Rh agglutinin has to be used to screen the population. Agglutination with Rh positive cells will occur only at 37°C when incubated over a definite time interval. This is rather cumbersome compared to routine typing for the classical blood groups.

Clinical features of incompatible transfusion: The rapid advances made in surgical techniques have brought in their wake, an increased need for transfusion. With more hospitals establishing blood banks to cater to their requirements, blood transfusion has become a very safe procedure which is employed repeatedly in the same patient and for most patients undergoing surgery of one sort or the other. It is incumbent on the part of every one trained in medicine, to recognise the signs and symptoms, at the earliest moment, of incompatible transfusion.

As a preventive measure, blood of the proper group is selected ideally in a painstaking and elaborate manner, avoiding even the suspicion of possible incompatibility. The rapidity with

which the transfused blood runs into the vein of the recipient, depends on the volume of blood lost. Except in the case of severe loss of blood, the transfusion rate should be about 500cc. over about 30 minutes.

Signs of incompatibility of transfused blood are evident very soon after a small volume of it has entered the recipient's circulation. These symptoms arise out of the blocking of small arteries, by masses of clumped blood cells. Headache, pain in the loins, tingling and numbness in the limbs, precordial distress are the earliest symptoms and should not be disregarded. If transfusion is continued in spite of these danger signals, suppression of urine by hæmoglobin from hæmolyised cells and other fatal sequelæ will ensue.

When only a small quantity of incompatible blood has entered the circulation, the clumped cells are hæmolyised and the released blood pigment may be passed through the kidney, causing hæmoglobinuria. Later, diuresis occurs. This is promoted by giving alkalis.

Aims in giving blood transfusion: 1. The primary aim is to restore the blood volume after hæmorrhage or surgery.

2. To increase the erythrocyte count, in anæmia.
3. To improve the coagulability of blood in diseases like hæmophilia, by supplying certain coagulation factors.
4. To stimulate hæmopoiesis.

PLASMA PROTEINS

Albumin, globulin, fibrinogen and prothrombin are the chief plasma proteins. The protein content in plasma is as follows :

Total proteins	—	6-8 gms % of plasma
Albumin	—	4.3-5 gms %
Globulin	—	1-3 gms %
Fibrinogen	—	0.2-3 gms %
Globulin	{ Euglobulin	— 0.1-0.4 gms %
	{ Pseudoglobulin	— 1-2.7 gms %
Albumin : Globulin	=	1.5 : 1

Fibrinogen occurs in greater proportion in some animals (dog, cow and goat). Globulin is more than or equal to albumin, in some animals. Relationship between plasma protein content and specific gravity of plasma :

$P = K (S - A)$ where P is plasma proteins in gms%, S is specific gravity and K is 364 and A is 1.006 (K and A constants).

The molecules of plasma proteins are sausage-shaped, all having nearly the same diameter—between 3.3 and 3.8 milli μ . They vary in length however, according to their molecular weight. The majority of pores in the capillary walls measure from 0.7 to 2 milli μ and some at least 3.8 milli μ . The largest of these allow the passage of albumin and larger molecules if they strike the capillary wall in the end-on position. This explains the small amount of proteins usually found in tissue fluid and urine.

Albumin: Mol. Wt: 70,000 to 75,000. It is a simple protein. It contains nearly all the known amino acids. It is soluble in water and dilute salt solutions and is coagulated by heat (75°C). It is denatured when heated near the iso-electric point and precipitated as a coagulum (test in urine). It is also associated frequently with small amounts of mucopoly-saccharides. It can be precipitated by complete saturation with ammonium sulphate and zinc sulphate.

Globulin: It is heat coagulable and soluble in dilute salt solutions but not in water. It is precipitated by half saturation with ammonium sulphate or by full saturation with magnesium sulphate. Saturation with sodium chloride throws out Euglobulin. It is also precipitated by half saturation with magnesium sulphate. Pseudoglobulin (soluble in water) is precipitated by saturation with magnesium sulphate or half saturation with ammonium sulphate. Electrophoresis separates globulin into alpha, beta and gamma globulins. Pseudo globulin contains 85% alpha globulin and 15% gamma globulin. Euglobulin contains less of alpha and more of beta and gamma fractions. The iso-electric points of alpha, beta and gamma fractions are 5.1, 5.6, and 6.0 respectively. The mol. wt of globulin is 150,000

to 200,000. Serum globulin is probably a single large molecule which is split into two or three separate fractions by laboratory manipulations. However, gamma globulin is increased in many acute and chronic infections and is intimately associated with antibody production. Prothrombin is perhaps beta globulin.

Fibrinogen : Very large molecule (500,000, m.w). It is precipitated by 25% saturation with ammonium sulphate. Fibrinogen has been isolated and crystallised. Fibrinogen is converted to fibrin due to the action of thrombin. Fibrin is insoluble. It is increased in pregnancy, menstruation, injuries, hyperthyroidism, infections and malaria.

Low protein content in plasma is the result of hæmorrhage and cirrhosis of liver. Albumin is reduced in chronic infections and nephritis. Globulin is increased in chronic and also acute infections, œdema, nephritis (an absolute or relative increase). Iso-agglutinins (anti A, anti B and Rh) are associated with gamma and beta globulins. Gamma globulin is increased in many chronic diseases, nephritis, tuberculosis and leukemia. Beta globulin and prothrombin are increased in late pregnancy. Hypoproteinaemia means a protein content less than 5.5 gms%. The electrophoretic fractions of plasma are not all pure but contain lipid and carbohydrate material, probably combined as prosthetic groups. 50% of lipids and carbohydrates of serum is bound to albumin and gamma globulins. Calcium, phosphorus etc. are bound to albumin fraction.

FUNCTIONS OF PLASMA PROTEINS

1. The maintenance of the colloidal osmotic pressure of blood by plasma proteins is of paramount importance in the regulation of blood volume. Albumin, being of the lowest molecular weight (70,000) among the blood proteins and occurring in the largest amount of all, is chiefly responsible for this function of plasma proteins, while fibrinogen with the highest molecular weight and much less concentration, is of minimal importance.

2. The viscosity of blood is due equally to the red cells and the plasma proteins. However, fibrinogen and globulin

contribute a greater share than albumin because of their greater molecular weight (larger molecular size). (See under blood pressure).

3. The erythrocyte sedimentation rate is influenced by fibrinogen and globulin. In infectious diseases, on account of a rise in their blood concentration, the red cells clump to a greater degree increasing the sedimentation rate.

4. Plasma proteins act as buffers in the maintenance of the acid-base equilibrium in blood.

5. Soluble fibrinogen undergoes a change to insoluble fibrin in the process of coagulation of blood (see The Coagulation of blood).

6. Plasma proteins serve as a body reservoir of proteins in states of starvation and also belong to the protein pool in the body which takes part in the amino acid transfers and their interconversions.

7. Immune bodies which develop in defence against infective micro-organisms, natural iso-agglutinins of blood groups and those put forth against extraneous blood groups, are associated with the gamma globulin fraction.

In tissue cultures, white blood cells prepare substances known as trephones from plasma proteins to nourish living cells grown in culture.

HÆMOGLOBIN

Hæmoglobin (Hb) is the orange yellow coloured pigment present in the RBCs. The functions of Hb are: 1) Carriage of oxygen from the lungs to the tissues. 2) Transport of CO_2 from the tissues to the lungs, to be eliminated. 3) Regulation of acid base balance of blood.

If there is no Hb and the oxygen transport were to be carried out only by plasma to meet the normal oxygen requirements of

the body, there should be about 350 litres of plasma in the body. The inclusion of Hb in the corpuscles gives certain advantages. If it were merely dissolved in the plasma, it would increase its viscosity and raise its osmotic pressure by 100 mm of Hg and so entirely derange the mechanism of water interchange between the capillaries and the tissue spaces. Further, free Hb is not only excreted by the kidneys but in the body itself is taken up and destroyed by the reticulo-endothelial system.

Hb is a conjugated protein—i. e.— a protein to which is attached some other substance known as the prosthetic group. It belongs to the group of chromoproteins. It is a conjugated protein consisting of histone globin which is the protein part united to the iron containing substance Hæme which forms the pigment part. Hæme is a protoporphyrin—i. e.— it is the combination of a metal with a porphyrin nucleus. The porphyrins occur widely in nature. So Hb is an iron-porphyrin-globin complex in which the iron is in the ferrous state. If the protein is denatured or ferrous iron is converted into ferric form, the respiratory function will be interfered with.

The most important property of Hb is its ability of combining with oxygen to form an easily dissociable compound called oxyhæmoglobin. This combination is not oxidation. The iron is in the ferrous state both in Hb and oxyhæmoglobin. Oxyhæmoglobin gives up oxygen very readily when exposed to low oxygen tensions.

One gram of Hb can combine with 1.34 cc of oxygen. 100 cc of blood contains on an average 15 grams of Hb (14–17 gms%). So 100 cc of blood can combine with nearly 20 cc of oxygen. This is known as the oxygen carrying capacity of blood.

Hb can also combine with CO very readily. In fact, the affinity of Hb for CO is 250 times that for O₂. The resulting compound is known as carboxy or carbonmonoxy-hæmoglobin. Though this union is also loose, it is more stable than oxyhæmoglobin. Carboxyhæmoglobin poisons the cytochromes and cytochrome oxidase which are the enzymes concerned in cellular respiration. As a result of the formation of carboxyhæmoglobin,

the ability of the blood to carry oxygen is diminished and the subject is in grave danger of anæmic anoxia. Because of the loose union, CO from carboxyhæmoglobin can be displaced by exposure to pure oxygen for a considerable time. The rate at which oxygen displaces CO is proportional to the pressure of oxygen. When CO is taken up by blood, it imparts a characteristic cherry-pink colour to the blood.

Hæmoglobin and its derivatives may readily be distinguished with the use of an instrument called Spectroscope, by their characteristic absorption spectra.

Normal values of Hæmoglobin in blood: Hb makes up about 35% of the dry weight of the red blood cell. The average Hb content of blood is a) in males—15.8 gms/100 ml. b) in females—13.7 gms. The average, irrespective of sex, is 14.5 gms%. At birth, the Hb content is about 23 gms%. It falls below normal levels by the end of the 3rd month. Then it gradually increases and reaches a value of 12.5 gms by the end of the first year. 1 gm of Hb, as mentioned before, can combine with 1.34 cc of O_2 . Hæmoglobin concentration is hence an index of oxygen carrying power of blood.

Estimation of Hb in blood: This is a commonly performed investigation in the diagnosis and treatment of anæmias. There are two methods.

- 1) Talquist's paper method—In this, a drop of blood is placed on a blotting paper and after drying, the colour is matched with standard colours of Hb corresponding to various percentages. This is a rough and ready method and the results are not very dependable.
- 2) In the second method, the Hb is converted to acid hæmatin and this is colorimetrically matched with the colour of standard acid hæmatin. 20 c mm of blood is taken by means of a capillary pippette. This is transferred to a comparison tube in which N/10 Hcl is taken upto the mark 10. In this tube there are graduations on both sides, one giving the percentage and the other in grams. Distilled water is added drop

by drop until the colour of the acid hæmatin in the tube matches with the colour of the standard acid hæmatin of the glass columns kept on both sides of the comparison tube.

HÆMOGLOBIN INDICES

- 1) Colour Index : This is a numerical expression of the Hb content of the red cell as compared with a normal cell. It is derived by means of the formula $\frac{\% \text{ Hb}}{\% \text{ RBC}}$. The normal range is 0.9 to 1.1. A value below this range indicates that each RBC carries less Hb than normally. Likewise, higher values signify greater amount of Hb in each cell on an average.
- 2) MCV—The mean or average corpuscular volume. It is obtained by finding the hæmotocrit value of the sample of blood and also the erythrocyte count.

$$\text{MCV} = \frac{\text{Packed cell volume in 1000 cc blood}}{\text{RBC count in millions/c. mm}}$$

Normally, an average cell has a volume of 90 $\text{c}\mu$. Microcytes have less volume and macrocytes have greater volume.

- 3) MCH—Mean corpuscular hæmoglobin

$$= \frac{\text{Hæmoglobin in 1000 cc of blood}}{\text{RBC count in millions.}}$$

Normal— 29.5 ± 2.5 micromicrograms ($\lambda\lambda$).

In hypochromia there is less hæmoglobin and in hyperchromia more of it than normally.

- 4) MCHC%—Mean corpuscular hæmoglobin concentration percentage. This is the amount of hæmoglobin in 100 cc of

$$\text{packed red cells. MCHC} = \frac{\text{Hb in gms in 100 ml}}{\text{PCV}} \times 100 =$$

(35 $\pm$ 3) G%

Varieties of Hb : The Hb of the foetus is different from the Hb of the adult. Foetal Hb is designated HbF and adult Hb is designated HbA. The difference lies in the globin moiety, the hæme being the same in both. Sick cell anæmia is a rare condition in which the RBCs assume a sickle shape. This is due to a defect in the globin part. The Hb in sickle cell anæmia is designated HbS.

BLOOD VOLUME

The total blood volume, circulating in the vessels of an adult amounts to 5 or 6 litres, which is about $1/12$ of the body weight. A few methods have been developed to estimate the blood volume in a human subject. An early method, a rather gory one, was to collect the blood from the body of a decapitated criminal, and measuring the quantity. To improve the accuracy, the blood vessels were washed out with normal saline and the washings were collected and by comparison with a standard suspension of blood in saline, the actual volume of the blood in the washings is derived and added on to that of the blood collected as such. Even so, it may not be possible to thoroughly remove all traces of blood from the minute blood vessels, especially the small veins. This procedure was employed in the beginning to arrive at an approximate estimate of the blood volume.

Obviously, an alternate, indirect method had to be resorted to for routine clinical purposes, in the case of human subjects. This is the dye dilution method of Keith and others, improved by Gregersen. The most suitable dye for this purpose is Evans blue (T-1824). This dye satisfies certain essential requirements to qualify for use in blood volume determinations.

1. It dissolves freely in plasma, imparting a blue colour to it. Slight degrees of hæmolysis will not introduce any errors.
2. The red cells and the endothelium of the blood vessels have no avidity for this stain which is wholly dissolved in plasma.
3. The dye does not pass through the walls of the blood vessels into the extravascular spaces, within the time taken for the determination.

4. It is also not rapidly excreted through the kidney in appreciable amounts.
5. No untoward effects arise from the use of the dye. The dye is innocuous.
6. Evans blue does not undergo chemical degradation in the body within the short span of time of removing of a few samples of blood.

A small quantity (5 or 10 cc) of blood is withdrawn from an arm vein and after adding an anticoagulant to it, it is centrifuged to find the packed cell volume (Hæmatocrit). The plasma is utilised to prepare a colour standard by dissolving a known amount of the dye in a measured volume of plasma.

A weighed quantity of the dye is dissolved in a small volume of water (5cc) and is injected into the same vein as was used for drawing the blood. Sufficient time is allowed for the dye solution to mix uniformly in the whole of the blood in the body. A sample of blood is drawn from the opposite arm vein, about 15 minutes after the injection of the dye. The plasma concentration of the dye in the sample is determined by comparing it with the standard prepared earlier. From the amount of dye injected and the concentration (actual dilution in blood in circulation) in the plasma sample, the volume of the plasma in the body can be calculated.

- W — weight of dye injected
 C — concentration of dye in the plasma of the sample
 V — volume of plasma in the body.
 $V = W/C$ litres.

Only when the dye mixes slowly in the plasma and there is a possibility of some of it leaving the circulation, it is necessary to take blood samples at intervals—at 10, 20, 30 and 40 minutes after the injection of the dye. The concentrations of the dye in the various samples are plotted against the times of sampling. The line joining the points is produced to the left to get the concentration at zero time. This value is used in calculating the plasma volume.

Knowing the packed cell volume (determined in the beginning) and the plasma volume (dye method), the total blood volume is derived.

- H — packed cell volume as percentage
 V — volume of plasma
 B — blood volume

$$B = \frac{V \times 100}{H} \text{ litres}$$

Plasma volume is also found by administering albumin tagged with labelled iodine - I^{131} . This has an advantage that milkiness of plasma—as when loaded with fats (lipemia)—does not interfere with the determination, unlike in the dye method. Dextran also has been employed in the place of tagged albumin or Evans blue. Haemolysis and lipemia do not vitiate the results in this case.

With regard to all the above procedures it is assumed that haematocrit values are the same in all parts of the circulation. It is not so. A more accurate method of blood volume determination would be to estimate the cell volume in the blood separately and add the plasma volume to it, to arrive at the blood volume. A 'O' group person is given orally an iron salt—ferri et ammonium citrate—in which the iron is radio-active. The red cells show maximum uptake of the iron in about 21 days. About 100 ml or less of this blood (O group) is transfused into the subject whose red cell volume is to be determined. Samples of the recipient's blood are obtained and centrifuged. The radio-activity of the donor's cells is compared with that of the recipient's cells and the cell volume of the latter is obtained. This is added to the plasma volume as estimated by the dye or I^{131} or dextran method.

As mentioned earlier, the entire blood in the body constitutes 1/12th of the body weight, the cells and the plasma each forming about half of the blood volume. Blood volume is related to the weight of the body as well as the body surface area (3 litres per sq. metre). The amount per unit area of the body surface is

more in men than in women, because of the larger number of red cells. Plasma volume shows no sex difference. In children, the ratio is less and reaches the adult value at about the 16th year of age. Conditions in which blood volume is increased are—

- a) Exposure to high environmental temperatures which causes, in the beginning, withdrawal of water from tissue spaces into the vascular compartment, in people with adequate reserves of water.
- b) Emotional excitement.
- c) Pregnancy—especially in the later months—rise occurs in blood volume by upto 20-30%. This provides a reserve against loss by bleeding during labour. Initially in pregnancy, there is a rise in plasma volume and later, cell production also increases.
- d) Some rise may occur in exercise because of greater cell count, though plasma volume may be reduced.

In the following conditions, blood volume is diminished.

- a) Severe bleeding (hæmorrhage) occurring over a short period of time, resulting in loss of whole blood.
- b) Diminished 'plasma' volume by loss of water—diarrhœa sweating and shock of burns.
- c) Loss of cells by hæmolysis, as in malaria.

EFFECTS OF HÆMORRHAGE

The severity of the symptoms will depend upon the amount of blood shed. If less than 30% of the volume is lost suddenly, there are compensatory mechanisms which are brought into operation. Water is rapidly absorbed from tissues to increase the blood volume.

When a large volume of blood is lost in a very short period, fainting and unconsciousness may come about suddenly. Pupils in the eyes will be dilated, sphincters are relaxed and convulsions

may occur leading on to death. In somewhat less severe cases, a restless mental condition may result. The individual feels weak and then dizziness, nausea and even vomiting may supervene. The pulse becomes very rapid and thready. The skin and mucosæ are pale, the extremities cold and moist. There may be generalised sweating. Eye sight may be impaired and response to sensory stimulation may be sluggish or even absent. There is air hunger in view of the diminution of oxygen carrying capacity and hence breathing will be fast and shallow. All these subjects need blood transfusion very promptly as a life-saving measure.

The effects of moderate hæmorrhage can be grouped under 'immediate and delayed effects'.

Immediate effects: 1. Blood clots plugging the injured vessels. The lysis of platelets causes the release of serotonin, a powerful vasoconstrictor, which brings about the contraction of the muscular coat of the injured blood vessels and thereby narrowing and closing of the mouths of the injured vessels. The fall in blood pressure consequent on the loss of blood, aids in preventing further hæmorrhage.

The signs and symptoms reflect the effects of compensatory mechanisms.

2. The fall in blood pressure brings about an increase in respiratory rate in an attempt to improve the oxygenation of blood, in the face of a lowered blood volume. This results through the stimulation of carotid and aortic baroreceptors, as well as hypoxia stimulating the chemoreceptors.

The fall in blood pressure (consequent to the loss of blood) brings about a rise in the rate of the heart by excitation of the pressoreceptors in the carotid and aortic regions. A rise in the pulse rate is a very valuable sign not only when it occurs in visible hæmorrhage, but also more importantly, in internal hæmorrhage. A fast pulse in an injured person, when there is no sign or external bleeding, should strongly suggest internal bleeding and this may be the only sign to go by.

A re-distribution of the blood takes place, diverting it from less vital regions to the brain and the heart. This is brought about not only by stimulation of baroreceptors in carotid and aortic regions, but also by the release of catechol amines. The re-distribution results in diminishing the vascular capacity so as to accommodate a smaller volume of blood. This ensures an adequate venous return and hence maintains the cardiac output. When the blood loss is somewhat greater so as to render the diminution of vascular capacity ineffective as a corrective measure, vasoconstriction occurs raising the blood pressure, even though venous return and cardiac output may fall. When even this means of maintaining the blood pressure fails in hæmorrhage of greater severity, blood pressure falls with attendant symptoms.

A rather rapid way of restoring the blood volume is by abstraction of water from the tissues into the blood vessels. This in turn, causes a sensation of thirst necessitating the drinking of water to replenish the body reserves of water. Hæmodilution is a corollary to this mechanism of making up the blood volume. In persons donating blood for transfusion (one pint at a sitting), the blood volume is restored in this way in about an hour.

Delayed effects: While the crisis of fall in blood pressure with consequent anæmia of vital organs, is tided over by immediate compensatory mechanisms as detailed above, attempts are in progress to restore the constituents of blood lost in hæmorrhage, to their normal proportion. Fibrinogen content of the blood is restored to the normal value within a day. The other plasma proteins are synthesised and in a few days to a few weeks, they regain their normal concentration. High protein intake facilitates this regeneration of proteins. The lost erythrocytes are gradually replaced over a period of two to three weeks or even more. The leucocyte count however, seems to be brought back to normal in a few hours after bleeding.

In cases of severe hæmorrhage, when the above-mentioned mechanisms are not adequate to meet the crisis, it is necessary to restore the blood volume by blood transfusion in appropriate amounts.

COAGULATION OF BLOOD

It is a very common observation that when blood is shed from the body, it solidifies in a few minutes and this change from the fluid condition to one of solid or semisolid state is known as coagulation or clotting.

If a small quantity of blood is taken in a test tube and allowed to stand for some time, the blood coagulates and even inversion of the test tube will not make the blood flow down. If some more time is allowed, a clear yellow fluid separates from the clot and this is known as serum, which is so to say squeezed out by the 'retraction' of the clot which consists of slender fibrin threads forming a very close mesh-work within which are trapped the cellular elements of blood. Under a microscope, the nature of a clot can be easily seen.

The most important of the various chemical changes that take place during clotting is the conversion of soluble fibrinogen to insoluble fibrin. Fibrinogen is a plasma protein occurring to the extent of 200 to 300 mgms in 100 cc of plasma. It is of the nature of a globulin and has a molecular weight of about 500,000. The molecule is spindle-shaped with its length very much more than its thickness. The enzyme, thrombin, causes the splitting off, of two polypeptide fragments - peptide A and peptide B - from the fibrinogen molecule which then polymerises end to end to form very fine fibrin filaments, a number of which come to lie side by side and are united to each other by side linkages. It is in this form that it becomes visible under the microscope and is known as a fibrin thread.

Thrombin: It is a protein belonging to the group of albumins. Its only action is to bring about the conversion of fibrinogen to fibrin. Thrombin is not present as such in blood. It is derived from prothrombin, a naturally occurring plasma protein. Prothrombin is a globulin and in the presence of calcium ions it is converted to thrombin by thromboplastin which may be an actual substance or more probably represents the action brought about by the coming together of a number of

coagulation factors. Vitamin K is known to be necessary for the formation of prothrombin in the liver. When vitamin K levels are low, synthesis of prothrombin is interfered with and its plasma level will go down.

Thromboplastin: It was originally considered to be an enzyme with a chemical identity and hence the name thrombokinase was in vogue. This term has now been given up. According to Morawitz, two chemical changes constitute the process of coagulation. One is the conversion of prothrombin to thrombin by thromboplastin and the other the conversion of fibrinogen to fibrin. There is universal agreement among all workers in this field about the occurrence of the above two reactions. It is with regard to the actual mode of formation of thromboplastin from a number of precursors and the actual sequence of steps involved, that there has been a great deal of speculation. In fact, of all the subjects in Physiology and Biochemistry, this has given rise to the most vigorous of controversies. To add to the confusion, different workers have employed different terms in referring to the same coagulation factors. It is in this context that an international committee was formed to do away with this multiplicity of terms. It is advisable for the student as well as for those having a casual interest in coagulation, to refer to the various factors, except a few very well known ones, by the international numerals assigned to them.

Tissue Thromboplastin: More than hundred years ago it was found by Howell and others that extracts of tissues when added to blood hastened coagulation. The tissue extracts were taken to contain an enzyme, thrombokinase, later called thromboplastin, which in the presence of calcium ions, brought about the conversion of prothrombin to thrombin. Macfarlane showed that two factors, one a protein and another a lipid, were involved in thromboplastic activity. Other workers suggested that more factors were needed for the formation of thromboplastin.

Blood Thromboplastin: When a small volume of blood was kept in a silicon-lined vessel or in a glass vessel coated with

paraffin wax, it did not clot, but when it was transferred to a glass container so as to be in contact with a water wettable surface, the process of coagulation was initiated and blood clotted in a short time. Before this observation was made, it was almost religiously held by many that tissue extract was absolutely essential for the formation of thromboplastin. The occurrence of clotting in glass vessels demonstrates that all the factors that are necessary for the formation of thromboplastin are present in blood itself.

From the foregoing lines, the conclusion is inescapable that there are two kinds of thromboplastin – 1) one which can be traced in its origin to tissue extracts—tissue thromboplastin or extrinsic thromboplastin.

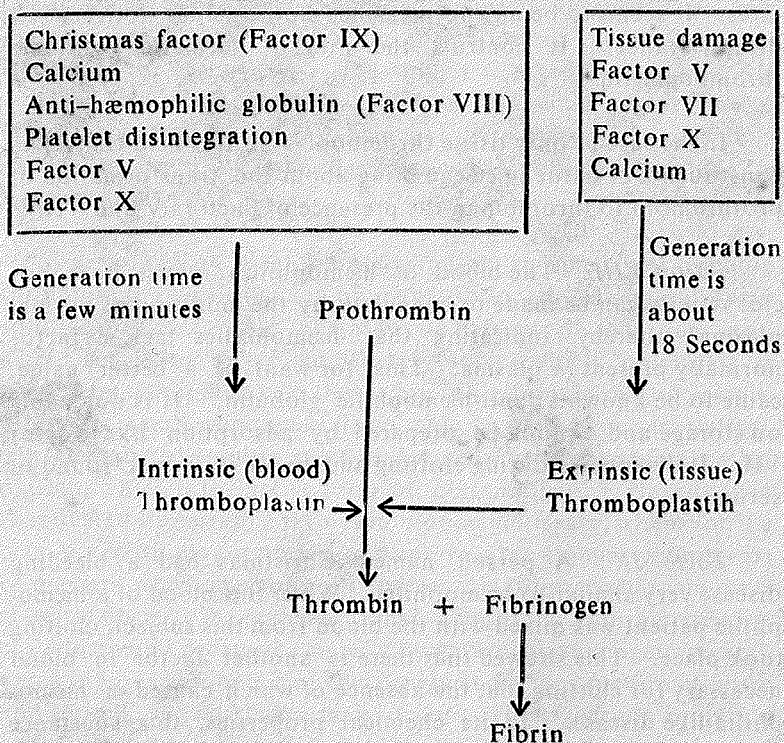
- 2) Blood thromboplastin—intrinsic thromboplastin, formed by a sequence of autocatalytic chemical changes. Macfarlane pictured the formation of thromboplastin as a series of pro-enzyme – enzyme reactions in which each enzyme activates the next, till the final stage of clot formation is reached. This view has come to be known as the Cascade hypothesis which has not been accepted by all workers.

INTERNATIONAL NUMBERING OF COAGULATION FACTORS

Factor	I	— Fibrinogen
Factor	II	— Prothrombin
Factor	III	— Thromboplastin
Factor	IV	— Calcium
Factor	V	— Labile factor of 'Quick'
Factor	VI	— Same as factor V, probably an active form of Factor V.
Factor	VII	— Stable factor.
Factor	VIII	— Anti-hæmophilic globulin.
Factor	IX	— Christmas factor.
Factor	X	— Stuart-Prower factor.
Factor	XI	— Plasma thromboplastin antecedent.
Factor	XII	— Hageman's contact factor.
Factor	XIII	— Fibrin stabilising factor.

Inspite of the international numerals coming into vogue, the terms like fibrinogen, prothrombin, calcium, anti-hæmophilic factor, X'mas factor etc. need not be dropped from use as they are better known than the numbers assigned to them.

The formation of thromboplastin of both varieties is indicated schematically below :—



Factor V: The discovery of this substance was made by Quick, when prothrombin in plasma stored for sometime was not converted to thrombin by tissue extract. Also, prothrombin prepared by adsorption and by salting out by half saturation with ammonium sulphate, could not be converted to thrombin by tissue thromboplastin. This showed the existence of a factor in plasma necessary for clotting but easily destroyed during storage. Factor V is used up during clotting and hence is not found in serum. Its concentration in plasma determines the amount of thromboplastin formed.

Factor VII: Prothrombin was found to need another factor for its conversion by thromboplastin (tissue extract) to thrombin. Patients treated for thrombosis with dicoumarin had a coagulation defect, thought to be due to lack of prothrombin. Addition of normal serum which does not contain prothrombin corrected this defect. This factor known as 'stable factor' is present in serum and can be prepared by adsorbing on to inorganic precipitates. It seems to be an enzyme, since clotting does not cause its disappearance. It controls the rate of formation of tissue thromboplastin.

In the case of only tissue thromboplastin, it is held that some constituents of tissue juice can bring about the transformation of prothrombin to thrombin in the presence of Factors V and VII.

Factor VIII: The blood of hæmophilics which does not clot rapidly can be made to coagulate by the addition of normal plasma, thereby indicating that hæmophilics lack a factor normally present in plasma. This, for want of a better name, came to be known as anti-hæmophilic globulin. It is not stable on storage and cannot be prepared by adsorption like Factor VII. It disappears during clotting and hence it is not found in serum.

Factor IX: A person named Christmas had a bleeding disease very similar to hæmophilia. When the blood of a hæmophilic patient was mixed with the blood from this subject, clotting took place. This showed that there is another factor in blood necessary for clotting, but the absence of which caused a hæmophilia-like disease. In its chemical properties, this substance resembles Factor VII.

Factor X: The importance of this factor was realised when certain patients who were treated with dicoumarin showed, in addition to lowering of prothrombin content of plasma, a fall in the level of Factor VII, X'mas factor and an unknown factor. In the last case, blood thromboplastin formation was interfered with, while in patients with insufficient amounts of Factor VII, blood thromboplastin generation was normal. Stuart Prower factor was the name given to the new factor whose synthesis was

depressed by dicoumarin. It is necessary for the formation of intrinsic thromboplastin. In persons having deficiency of Factor VII, caused by dicoumarin administration, there is no interference with formation of blood thromboplastin and hence it follows that factor VII is not a component of intrinsic thromboplastin.

Factor XI: (PTA): Another hæmophilia-like condition which affects either sex has been discovered recently. A new factor seems to be needed for the formation of blood thromboplastin, in the early stages. Possibly, it is acted on by factor XII which in its active form is derived from Hageman factor (Factor XII) when blood comes into contact with glass. In chemical properties, factor XI resembles factor VII, while factor XII is like factor V.

Factor XIII: When pure fibrinogen is acted on by pure thrombin, the resulting clot of pure fibrin threads dissolves in solutions of urea, while fibrin formed from plasma does not. There seems to be an additional factor which, once clot is formed, makes it stable so that it can plug injured blood vessels. Normally, small amounts of fibrin may be formed in circulation. This is rendered soluble as it is formed, by an enzyme called plasmin which is the active form of plasminogen. Plasminogen is activated by certain enzymes in blood and tissues, when clotting occurs. With the formation of fibrin in large amounts, inhibitors of plasmin which are normally present in appreciable amounts stabilise fibrin. In some abnormal conditions (during surgery, child birth and prostatic cancer) however, plasminogen is activated in large amounts and this brings about destruction of fibrin and serious hæmorrhage may occur. There occurs in blood normally, a substance which inactivates plasmin as it is formed and in addition another substance which inhibits such agents as may inactivate plasminogen. Thus, it appears that there is a delicately balanced system of factors, one to bring about dissolution of fibrin and the other to stabilise it.

Though all the factors enumerated and described above, may each play a role in coagulation, yet the sequence in which the various substances react with each other is still very poorly understood. Several schemes indicating possible changes and

conversions that take place among the various substances involved in clotting, have been described. In general, the earlier reactions are concerned with the formation of thromboplastin of the one kind or the other. In the case of blood thromboplastin, it is likely, though not proved, that contact with a 'water wettable surface' triggers off the subsequent reactions. Though initially, 'water wettability' of a surface was thought to be a significant factor, yet, since vascular endothelium is also wettable, it is to be wondered what exactly is the difference between the glass surfaces which promote clotting and endothelium which does not. It has been suggested that some plasma factors may be adsorbed on to the glass surface which then sets off the subsequent changes, leading to the formation of intrinsic thromboplastin.

Calcium: The importance of calcium ion in clotting follows from the fact that, if calcium is removed from plasma by the addition of citrates or oxalates, clotting can be prevented. From in vitro studies, it is now known that calcium is necessary for the formation of thromboplastin as well as for the conversion of prothrombin into thrombin. Fibrinogen is converted to fibrin in the absence of Ca ions. It has to be noted that decalcifying salts like citrates and oxalates have to be added to blood immediately after it is drawn from the body, so as to prevent the formation of thromboplastin. If a few minutes elapse between the drawing of blood and the addition of salts, coagulation may still occur.

Calcium may be adsorbed by various proteins in the plasma and may provide surface charge necessary for the interaction of various factors.

Viper venom does not need ionic calcium for its coagulating action on blood and so also trypsin.

Platelets: The platelets which are known as thrombocytes because of their importance in clotting, seem to control the amount of thromboplastin formed, but not the rate of its formation. Since brain extract (tissue extract) can substitute for platelets, it is most likely that platelets contribute a phospholipid.

In tissue extracts, cephalin seems to be the substance involved. Platelets promote clot retraction — the meshwork formed by the fibrin threads becomes compressed by the action of platelets which adhere to fibrin threads, especially where they cross each other. Retraction of clot makes the clot firm and also brings about the separation of serum. In thrombocytopenia, because of a low platelet count, clot retraction is delayed. Even trivial injuries may lead to prolonged bleeding. In addition, in this condition, there seems to be an abnormality in clotting too. Bleeding time is prolonged in thrombocytopenia. The term purpura is applied to this condition in view of the small petechial hæmorrhages under the skin, which characterise the condition. Even ecchymoses or wide areas of bleeding may be seen. The spleen is usually incriminated as the cause for increased platelet destruction and consequent low count. Splenectomy has been performed in thrombocytopenic purpura, as a curative measure.

Hæmophilia: This occurred as a familial disease in some royal families in Europe, especially of the former Spanish ruling house. It is transmitted of means of a sex-linked gene. In other words, the X-chromosome carries this abnormal gene. It is the mother who transmits this condition to her son. While the daughter may inherit this defective chromosome, she does not suffer from hæmophilia. The daughter will be an active sufferer if her mother is a transmitter and her father is a sufferer himself. The diagnostic feature is a lengthened coagulation time. Even after minor injuries or sometimes, apparently spontaneously, the afflicted individuals bleed and lose large amounts of blood. Bleeding into the cavities of the body and joints may often occur. Rarely, a family history may not be forthcoming. Treatment is by providing the specific coagulation factor that is lacking in these people, namely the anti-hæmophilic globulin. Transfusion normal blood, but of the same group as the patient, promotes clotting. Plasma can be used instead.

Subsequent to the recognition of the underlying causes of hæmophilia, another condition closely resembling it, was discovered and this is Christmas disease; a factor going by the

same name was found to be lacking, in this disease. Normal serum can be given, since the Christmas factor is present in serum and is not used up during clotting.

Tests used to detect coagulation defects: The earliest test was to determine the whole blood clotting time, which can be done in two ways. A small quantity of blood (a few ccs) is kept in a test tube after having been drawn from a vein. The time necessary for clotting is noted. The exact moment of clotting can be found out by inverting the tube, when blood will not pour down. This is a very crude way of determining the clotting time. Alternatively, the finger is pricked and the drop of blood that comes out is drawn into a capillary glass tube. Bits of it are broken at 15 second intervals. When clotting occurs, the bit broken off will not fall away. On attempting to pull the fragment away, a thread of clotted blood can be seen to bridge the gap. The moment when this occurs, gives the clotting time. The normal clotting time is a few minutes (within ten minutes).

A lengthened whole blood clotting time does not indicate the exact defect in the clotting mechanism. The lack of any one factor necessary for the formation of blood thromboplastin, can prolong the clotting time. In view of this serious shortcoming of the test, other more precise tests have been evolved to test for the lack of any one of the clotting factors. Another time honoured procedure is to find the so called prothrombin time, as was devised by Quick. This procedure attempts to indirectly measure the prothrombin content of plasma. Citrated plasma is kept in a test tube in a water bath maintained at 37°C. Excess of tissue thromboplastin and the necessary amount of calcium are added to the plasma and the time for clotting is noted.

Thromboplastin generation test: This is a precise test. The various coagulation factors can be prepared, each separate from the others.

The presence in adequate amounts or otherwise, of any one of the factors, can be detected by means of this test. The particular factor whose concentration has to be assessed, is supplied by the plasma of the subject under investigation. The

other factors are prepared separately from normal plasma. The various factors are mixed in the proper proportion and incubated at 37°C. Once in every few seconds, a sample from the mixture is taken and added on to a mixture of pure prothrombin and fibrinogen. The clotting time is inversely related to the amount of thromboplastin formed. If the plasma under test is deficient in more than one of the factors, the test can be repeated to determine the adequacy or otherwise of each of these. Once thromboplastin is formed in sufficient amount in the incubated mixture, the prothrombin fibrinogen mixture clots in about 10 sec. The time of incubation necessary for the formation of thromboplastin in adequate amounts, provided all the factors are present in proper proportion, is about 3—6 mts. This test naturally cannot be performed as a routine, but precise information can be obtained from this.

It takes about 20 seconds at the longest for the generation of tissue thromboplastin, under standard conditions. On the other hand, the development of blood thromboplastin takes about 3 minutes or more. Thus, it will be seen that it is the preliminary stages in the clotting process which are time-consuming. The conversion of fibrinogen to fibrin, once thromboplastin is formed, is an explosive or an instantaneous change. In tests described above, the truth of this statement can be very well appreciated. For some minutes, there is apparently no change, but all of a sudden clotting has taken place.

ANTI-COAGULANTS

Anti-coagulants have been used for many years, both to preserve blood in a fluid condition, in the laboratory, as well as to prevent intravascular clotting or thrombosis. Anticoagulants which are to be used *in vitro*, i.e.—to prevent clotting of blood kept in vessels, are added to blood. The preserving of blood in silicon-lined vessels or wax coated glass vessels, is a well known practice. Cooling blood to retard the coagulation process, has also been in vogue. The easiest and the most convenient way of preventing coagulation of shed blood is by adding sodium citrate in sufficient amounts. Coagulation is prevented because calcium ions that are necessary for the early

stages of clotting are removed from the solution due to the formation of a complex salt—namely sodium calci-citrate. Potassium and ammonium citrates can also be used. But sodium salt is preferable, since it is cheaper and also if the preserved blood is used for transfusion, it will not disturb the extra-cellular electrolyte balance. Oxalates of sodium and potassium also bring about decalcification of plasma by causing precipitation of calcium oxalate. Oxalates are not to be used as anticoagulants in view of their toxic nature.

Neutral salts have also been added to blood. Magnesium sulphate postpones coagulation. Zinc sulphate and sodium sulphate have also been used. The mode of action of sodium sulphate is not known. Zinc sulphate precipitates fibrinogen. 10% sodium chloride has been used. All these salts, excepting zinc sulphate, may prevent the lysis of the platelets. Dilution with water of blood, to which the salts have been added, will cause clotting.

Heparin has also been used to preserve stored blood. The nature of action is described below. When blood, as it is kept in a vessel, is vigorously stirred with a brush or a glass rod, fibrin threads can be collected around the brush or rod and removed. This cannot strictly be called as preventing coagulation. Fibrinogen has only been removed, leaving the rest of the blood in a fluid condition. However, the formation of a clot as such, consisting of a mesh work of fibrin threads entangling R. B. Cs is prevented.

Anticoagulants used in the treatment of intravascular clotting :

The incidence of coronary thrombosis and thrombosis in other parts of the body, is increasing day by day. Hence the use of anti-thrombotic agents has assumed importance in modern medicine. Heparin can be used intravenously to prevent intravascular clotting. Heparin is a mucopolysaccharide which is synthesised by mast cells found in the liver (hence the name heparin) as well as in the walls of small blood vessels or even the endothelium. The heparin content of a tissue is related to the number of mast cells in it. Heparin prevents coagulation, both

in vitro—when it is added to blood in a container and in vivo—when it is administered by injection. When given orally it is not absorbed easily. The action of heparin seems to be due to a strong electronegative charge held by it on account of its sulphuric acid groups. Substances like Toludin blue, possessing positive charge, annul the action of heparin. Heparin acts on more than one stage in the coagulation process. It prevents the formation of thromboplastin by occupying the reactive sites of the protein substances involved in coagulation, as well as by preventing lysis of platelets. Formerly, it was described as having an antithrombin action thereby blocking thrombin action on fibrinogen. It is presumed that small amounts of thrombin are always being formed in circulation and that it is inactivated then and there by a substance called antithrombin which is of the nature of an albumin. The action of heparin in neutralising thrombin, was thought to need the presence of antithrombin. It is possible that the presence of heparin in the mast cells of the walls of the small blood vessels may be responsible for maintaining the fluidity of blood which flows rather sluggishly in these vessels compared to larger arteries. Slow flow of blood is said to be conducive to intravascular clotting or thrombosis.

Dicoumarol: It was found in Canada some decades back that cattle which grazed on 'sweet clover' hay, developed symptoms of bleeding. Dicoumarol was isolated from this vegetable source. It can be given orally as well as by injection. Its anti-coagulant action is indirect. It interferes with the synthesis of not only prothrombin, by substrate competition with vitamin K but also Factor VII, Stuart-Prower factor and X'mas factor. Dicoumarol is ineffective as an anti-coagulant in vitro. A number of synthetic analogues of dicoumarol have been prepared and are in use.

Substances which promote clotting-Hæmostatics: Tissue extracts, venoms of certain snakes (Russel's Viper) and trypsin are sometime used to promote clotting. Thrombin may be used to prevent oozing of blood from wide areas. Horse serum can also be used (coagulen-ciba). Locally, sodium alginate and gelatin sponges have been used to promote clotting.

Thrombosis or Intravascular clotting: Normally, blood does not clot in any part of the circulatory system. Certain abnormal conditions seem to be responsible for thrombosis. The most important in this regard is damage to vascular endothelium. As long as the vessel lining is smooth and not abraded, there does not seem to be a chance for thrombus formation. Platelets are attracted towards an injured endothelial area. As more and more platelets adhere together, a white clot forms; later fibrin threads appear and red cells may get caught in the fibrin meshes. The thrombus, as the mass of platelets, fibrin and red cells is called, grows in size with a free tail projecting into the lumen of the blood vessel. The thrombus may block the blood vessel. If such an event occurs in the coronary arteries, coronary thrombosis may ensue. Fragments of the thrombus, if detached, may be carried to the other parts of circulation as 'emboli'.

It is not very clear as to how normally, thrombosis is not allowed to take place. Several possibilities can be thought of in this connection, some of which have already been considered.

1. The presence of an antithrombin readily neutralising thrombin forming in small amounts.
2. The smoothness of the endothelial surfaces.
3. The rapid flow of blood avoiding stagnation in blood vessels.
4. The action of plasmin in disposing off the fibrin as it is formed.
5. Presence of mast cells laden with heparin, in the walls of blood vessels, this acting as a safeguard when by any chance, blood flow becomes sluggish.

THE ORIGIN OF BLOOD CELLS

The mode of origin of blood cells is still a matter of some controversy. While regarding the later stages of development of blood cells there is wide agreement, the earlier ones form the subject of acute disagreement. To make matters

worse, there is a sharp divergence in the terminology used with reference to the various precursor cells in the erythroid series. In an account primarily meant for beginners in hæmatology, it is advisable to stick to one set of terms and become thoroughly familiar with it before trying to find parallels between different nomenclatures. British terms for various cells have one merit in that, only one name is used for three successive stages with a qualifying word preceding it and thereby making it easier to remember. What follows, mostly represents the views held by various authors as described in that classic of Hæmatology by Whitby and Britton (1953).

Blood cell formation in the embryo: In the first two months of embryonic life, this function is subserved by the 'area vasculosa' of the mesenchyme of the yolk sac and later in the placental site as well as body stalk. This is called the 'mesoblastic phase' which is followed by the 'hepatic phase' lasting from the third month to the fifth month of intra-uterine life. The liver, spleen and thymus are actively engaged in the formation of blood cells. From the sixth month onwards, the bone marrow gradually takes over this function and the 'myeloid stage' is said to have come into being. Hæmopoiesis, from now onwards is the function of the bone marrow (myeloid phase), the other tissues and organs giving up their functions completely, though over an extended period of time.

In the embryo, in the beginning, primitive mesenchymal cells form groups known as the 'Islands of Pander', each one of which forms a syncytium. The inner ones detach themselves from the others and form the primitive blood cells which acquire hæmoglobin and are known as primitive megaloblasts, which are nucleated cells. These in turn divide into daughter cells with increased hæmoglobin content. These are considered by Ehrlich to be relics of pre-mammalian origin. These cells are found in embryos less than 10mm length. It may be stated that in the early embryo, all the hæmoglobin carrying cells are nucleated. By about the 8th month, the vast majority of oxygen carrying cells are non-nucleated. The percentage of non-nucleated red cells indicates the age of the embryo.

In older embryos (longer than 10 mm), cells known as 'Definitive Megaloblasts' occur in the blood stream. They are smaller than the primitive megaloblasts, with a darker stained nucleus which is also smaller than those of the other megaloblasts. The megaloblasts (term given to a large hæmoglobinised, primitive nucleated cell present in embryo and in pernicious anæmia, but not in normal adults) of pernicious anæmia are considered to be descendents of the definitive megaloblasts.

The white blood cells, according to Sabin, are seen even from the 3rd day of fœtal life. They arise extravascularly in the mesoderm and enter the blood stream. Leucopoiesis is seen in liver in the beginning, but later, bone marrow takes over this function.

While red cells are appearing in the yolk sac, blood vessels develop in the embryo proper as well as in the yolk sac. The two systems meet each other and cells from the yolk sac flow into the embryonic vessels.

Much discussion has arisen in respect of two fundamental questions relating to the formation and development of blood cells. These are: 1) Whether all the blood cells—RBCs, WBCs and platelets are the descendents of a single parent or 'stem cell'? This implies that the maintenance of the cell population, both as regards their absolute numbers as well as their relative proportions, is due to the differentiation of only one kind of 'stem cell' into various types and development along separate lines, once differentiation has taken place. 2) Whether each kind of blood cell is derived from a different 'stem cell' which cannot under any circumstances give rise to the other blood cells? The view implied in the first question has been known as the 'monophyletic origin' of blood cells. According to the 'Polyphyletic origin' of blood cells (if true), each kind of cell has an ancestor different from those of others. A compromise between these two extreme views is that of the 'Dualistic origin' according to which all myeloid cells (arising from bone marrow) including red cells, granulocytes among the white cells and megakaryocytes, have a common ancestor or stem cell, while the

lymphoid cells—lymphocytes and monocytes—are derived from another. Each stem cell cannot produce the other types of blood cells.

There is however, a common area of agreement between the 'monophyletic' (unitarian) hypothesis and that of multiple or polyphyletic origin of cells. In the early embryo, mesenchyme gives rise to a primitive free cell, from which all future stem cells and blood cells are derived. The reticular cells of marrow and lymphoid tissues in adults are derived from mesenchymal cells.

Another venue of disagreement is regarding the exact site of origin (whether intravascular or extravascular) of the red and white cells. The experiments of McCulloch and others, in which normal marrow cells from a healthy mouse have been injected into other animals of the same species whose marrow has been rendered aplastic (inactive as regards hæmopoiesis) by irradiation, have shown that all myeloid elements have a common stem cell. Whang, from his chromosomal analysis of blood cells, has also drawn the same conclusion. It appears from these recent investigations that most probably, blood cells have a dual origin in that, myeloid elements are derived from one kind of stem cells, while lymphoid elements owe their inception to another progenitor. In this connection, it must be said that stem cells, while differentiating to give rise to different types of blood cells, do also produce stem cells again so that the formation of blood cells can go on throughout life and not come to an end abruptly, as would happen if stem cells are exhausted. Cell renewal is the term used for the replacement of stem cells by daughter stem cells to maintain hæmopoiesis. Gilmour is, of the opinion that in human embryos longer than 50 mms, erythropoiesis is extravascular and most authorities concur with his opinion that both red cells and white cells have extravascular origin, at least in the human subject.

The bone marrow: The bone marrow as an organ of red cell formation occupies a volume of 70ml. at birth, expanding to about 1400ml. in an adult. The weight of bone marrow in an adult may range from 1500 to 3500 gms. In the adult, only half of the marrow is active, the other half though inert can be

activated if necessary. While anoxæmia seems to be a stimulus for red cell formation, the spleen may also have some role (though not known at present). The sympathetic nervous system may control marrow activity.

Active bone marrow is red in colour, while inactive marrow is yellow and fatty. At birth, all bones contain red marrow. At about the 7th year, the marrow in the shafts of long bones becomes inactive. By about the 20th year, marrow of flat bones and proximal ends of long bones only is engaged in red cell production. But if there be necessity for increased erythropoiesis, yellow marrow can resume its function. Thus, the adult has plenty of reserve to meet an increased demand for red cells. In children, the entire bone marrow is active and thus there is very little reserve. Liver and spleen may be called upon to form red cells, if an occasion arises for the resumption of such a function. It is for this reason that children are more vulnerable to loss of blood by hæmorrhage. In old age, even some flat bones exhibit yellow marrow. The bone marrow also is involved in the formation of granulocytes and megakaryocytes. Destruction of aged red cells is carried out by the cells of the reticulo—endothelial system in the marrow in addition to those in other situations.

The Erythroid Series: The circulating red cells, as they are formed and developed from the parent cell, namely the hæmocytoblast (stem cell), pass through several stages, each one of which can be fairly accurately identified by certain characteristics. The naming of the different stages in different countries has led to more than one term being used to refer to the same stage in the development. In the following account, the terminology of the British Hæmatologists has been adopted for a few reasons given further on. It is purposeless for a beginner in hæmatology to try to learn all the parallel terms used for identifying the stages. Correlation of one set of terms with another is not a rewarding exercise. On the other hand, it is frustrating. The term, megaloblast, used to refer to the earliest recognisable member of the red cell series, is objectionable since this term is also employed in respect of an abnormal cell seen in pernicious anæmia. The descendants of such a cell form an abnormal megalocyte series. The British nomenclature for the

various stages in the development of the erythrocytes has one merit — namely — only one common term is used for three successive stages though each stage is identified by a qualifying term added on, like early, intermediate and later. The American terminology is not so simple.

Stage I—Pro-erythroblast: This is the earliest of the differentiated cells in this series, and it is of a large size (15 to 20 μ). The cytoplasm is deeply basophilic, with a narrow crescentic pale portion surrounding the nucleus which itself is very large (about 12 μ). Several nucleoli and a fine reticulum are characteristic features. Mitosis occurs at this stage to yield subsequent stages. The megaloblast of pernicious anæmia corresponds to the pro-erythroblast. It is very likely that the lack of Castle's anti-anæmic principle or vitamin B₁₂ is responsible for the conversion of the hæmocytoblast into a megaloblast. Normally, however, vitamin B₁₂ seems to promote the change to the pro-erythroblast.

Stage II—Early Normoblast: This is a smaller cell, capable of active division. The nucleus is devoid of nucleoli and the fine chromatin reticulum shows tendency to condense at some points.

Stage III—Intermediate Normoblast: There is further reduction in the size of cells, compared to the earlier ones. Mitosis can still occur. The nucleus shows further condensation. Hæmoglobin appears in the cytoplasm in traces at the beginning and later, in larger amounts. The cytoplasm shows dual staining and is said to be polychromatic—both acidophilic and basophilic. The size of the cell is 10 – 14 μ .

Stage IV—Late Normoblast: The size (7–10 μ) is less than that of the previous stage. The nucleus is very much condensed and is very dark in appearance when stained and is hence called pyknotic. Hæmoglobinisation has progressed to such an extent that the whole cell is now eosinophilic. Extrusion of the nucleus or its disintegration converts the late normoblast to a reticulocyte. The late normoblast cannot give rise to daughter cells.

Stage V—The reticulocyte: It is so called owing to the presence of a network of matter stainable with cresyl blue,

representing probably the remnants of basophilic cytoplasm. Reticulocyte normally constitutes 1% of the circulating red cells. In conditions of enhanced erythropoiesis, as happens with treatment using hæmatinics, the reticulocyte count increases. This is known as a reticulocyte response and indicates increased rate of red cell formation.

Reticulocytes and their subsequent forms, namely adult red cells, are the circulating forms of red cells. The primitive red cells, if at all found in circulation, occur in a very very small number. The suffix 'blast' suggests that the cell is a nucleated one and is confined to the bone marrow. A question has been raised as to whether the non-nucleated red cell is a living cell. Only one point has to be mentioned in this regard. If the red cell is to be considered as dead, on account of its being deprived of a nucleus, it has to follow that it cannot survive in circulation for long. On the contrary, the life span of red cell in circulation has been estimated to be about 120 days. No non-living structure can last as long as this. Further, the red cell is able to take part in respiratory and other activities like glycolysis, on account of the presence of substances like DNA and RNA as well as respiratory and other enzymes.

Certain facts concerning the development of the red cells through the various stages have to be highlighted.

- 1) As the cell passes through various stages, it diminishes in size from 20μ to $7-8\mu$.
- 2) The nucleus becomes progressively smaller and smaller, getting condensed in the process and finally becoming pyknotic, before its expulsion from the cell or disintegration within the cell.
- 3) In the beginning, the cytoplasm is strongly basophilic, indicating total absence of hæmoglobin (which is eosinophilic). Hæmoglobin is acquired during the stage of intermediate normoblast. The cytoplasm is converted to the acidophilic type with more and more hæmoglobin being deposited in it. The adult red cell is wholly eosinophilic.

It may be mentioned in conclusion that the development of the cell from the proerythroblast stage to that of the adult red cell, take about 4-5 days in all.

It follows that for replenishing the erythrocytes lost by wear and tear and in order to maintain a constant count in circulating blood, multiplication by mitotic division can take place only in the case of earlier erythrocyte precursors.

Leucopoiesis: The evidence already presented, has led to the more or less definite conclusion that the granulocytes are produced in the bone marrow along with the red cells with which they form the myeloid series. The lymphatic cells develop in lymphoid tissue—lymph nodes, spleen, thymus, Peyer's patches in the intestines.

The white cells of the myeloid series are descendents of the branched reticulum cells in the bone marrow. These cells divide mitotically to give rise to what is called a primitive white cell which in turn develops into a myeloblast (12-18 μ) with a blue staining cytoplasm forming a narrow rim around a pale large nucleus. It is in the next stage that differentiation into the three kinds of precursors for the granulocytes takes place, this stage being named as that of Myelocyte (neutrophil, basophil and eosinophil). The cytoplasm in these cells is greater in amount with less marked basophilic reaction. A premyelocyte (myelocyte A) stage in between the myeloblast and myelocyte, has been described. The myelocyte in which granules appear (granules of one of three kinds—neutrophil, eosinophil or basophil), develops into metamyelocyte which finally is converted to the circulating form of granulocyte. The stages in the development of the granulocyte are schematically represented below :

Reticular cell $\rightarrow$ Primitive free cell or hæmocytoblast $\rightarrow$
Myeloblast $\rightarrow$ Premyelocyte (myelocyte A) $\rightarrow$ Myelocyte (B & C)
 $\rightarrow$ Metamyelocyte $\rightarrow$ Adult cell.

The lymphoid cells develop as follows :

The lymphoblast which may be derived from undifferentiated

primitive reticular cells in the lymphoid tissue, develops into a large lymphocyte which matures and ages, changing into the small lymphocyte.

The platelets are said to be formed by the breaking off of the small pieces of cytoplasm from the large multi-nucleated megakaryocytes present in the bone marrow. The origin of monocytes is again the subject of controversy. They may arise from tissue cells in the spleen and marrow and therefore, are considered to belong to the reticulo endothelial system. Some authors take them to be descendents of lymphocytes.

LEUCOCYTES

These are commonly known as white blood cells. They are not white but merely colourless. Unlike erythrocytes, these are of a variable shape and size. But in an inactive form, they ordinarily have a spherical shape. Normally, in blood, they occur in numbers ranging from 5000 to 10,000/cubic mm. Exercise increases the count. After meals and in the later months of pregnancy, a rise in the WBC count occurs. The term leucocytosis means a rise in count, while leucopenia signifies a fall in count of WBC. The count is high in new born infants, which gradually declines and normal adult values are seen after the 5th year of age. The white cells are usually considered to be of five varieties – neutrophils, eosinophils, basophils, large and small lymphocytes and monocytes. The first three kinds are also collectively known as granulocytes. Lymphocytes and monocytes are conventionally called agranulocytes, because of the absence of granules in the cytoplasm when routine staining procedures are adopted. The agranulocytes exhibit coarse granules (lymphocytes) and fine ones (monocytes) when Azure stains are used. The different kinds of white cells occur normally in certain fairly constant proportions in relation to each other. Thus, neutrophils account for 50–70% of all the leucocytes, Eosinophils 1–4%, basophils about 0–1%, lymphocytes 20–40% and monocytes 2–8%. In children, lymphocytes form 40–50% of all the white cells.

Neutrophil: This is also known as the polymorphonuclear leucocyte (abbreviated to Polymorph), on account of the occur-

rence of a varying number of lobes (1 to 5) in the nucleus of the cells. The youngest form of this cell is known as the Band Neutrophil. As the cell grows old, constrictions appear in the nucleus giving rise to the formation of more and more lobes which are connected to each other by strands of chromatin. The percentages of different stages of the neutrophil identified by the number of lobes in the nucleus of the cell constitute the Arneth Index. Usually, the figures are—for cells with single lobed nucleus—5%, those with two lobed nucleus—30%, those with 3 lobes in the nucleus—45%, cells with 4 lobes—18%, cells with 5 lobed nucleus—2%. When the neutrophil count is reduced for any reason (typhoid, kala-azar, heavy metal poisoning etc.), the older forms predominate and there is said to be a shift in the Arneth Index to the right. When neutrophils are formed in large numbers, as in acute bacterial infections, the younger forms occur in larger numbers and Arneth Index shows a shift to the left. 'Schilling Index' is similar to Arneth Index, but it takes into account the precursors of neutrophils in the bone marrow also. The term agranulocytosis is applied to the reduction of neutrophils, resulting from the use of certain drugs in former days, like gold salts. The neutrophil is a very actively motile cell of a diameter $10-14\mu$. The cytoplasm shows fine violetish or red-brown granules. The term neutrophil is a misnomer. The granules are not really neutrophil in staining reaction. They take up both acid and basic stains and therefore were in the beginning, erroneously called neutrophil, which name has persisted. The cell has the remarkable property of phagocytosis and hence serves the function of protection against bacterial infections. Wherever there is a nidus of infection, neutrophils are attracted to it in large numbers. They arrive at the site of infection passing through the walls of neighbouring capillaries by a process known as 'diapedesis'. The cells push their pseudopodia in between the endothelial cells of the capillaries and through the pseudopodia, the cytoplasm of the cell flows out, the cells coming out of the blood vessel. The neutrophils are said to be attracted by a mysterious chemical force, namely chemotaxis, to the site of infection where they actively engage themselves in engulfing the infective organisms. An examination of such neutrophils may shows many of them containing a large number of bacteria trapped within their cell boundaries. Digestion of the bacteria

may occur later on. Sometimes, the neutrophils succumb when they are each confronted with an excessive number of organisms. Even so, as they die, they release proteolytic enzymes which are lethal to the organisms. When the neutrophilic response is adequate they wall off the infected area and thereby prevent the spread of infection.

An additional function of neutrophils is the removal of effete organs like the tail of a tadpole, during metamorphosis in a frog.

High neutrophilic counts occur in acute and severe infections by pyogenic organisms. The total WBC count thereby is raised to figures like 20,000 or more per cu. mm. Very high total WBC counts are seen in leukæmic states, the increase being due to a rise in the numbers of any one type of leucocyte. The counts may be as high as 100,000 and more. The predominance of primitive leucocytes in the peripheral blood is the hall-mark of leukæmia.

Leucopenia or a reduction in the total WBC count is mainly a reflection of a fall in the number of neutrophils. It is always a pathological condition. Common causes are typhoid fever in the later stages, kala azar and toxicity resulting from excessive dosage of heavy metal salts—gold, mercury, arsenic etc.

Eosinophil: This is a cell of the same size and shape as the neutrophil. The cytoplasm when stained with Leishman stain, exhibits many coarse, refractile, pink granules completely filling the cell and sometimes even obscuring the nucleus which has most often, two lobes connected by a fine chromatin strand (spectacle shape) and less commonly, a single lobe. The eosinophilic count is increased in infestation with worms, in allergic conditions like bronchial asthma, and hay fever and also in certain skin diseases. The granules are rich in histamine. It is not possible to pinpoint the functions of the eosinophil. While this cell has phagocytic properties though not to the same degree as the neutrophil, it appears to be involved in a detoxifying process, especially when foreign protein finds its way into the body.

Basophil: This third variety of granulocyte is somewhat smaller in size than the other two, with large single-lobed nucleus of irregular shape. The cytoplasm shows a few coarse darkly staining basophilic granules which contain heparin and serotonin among other substances. Local action in preventing coagulation of blood, especially when blood flow is slow in small vessels, may possibly be a function of this cell. The presence of hyaluronic acid in the granules may also serve to provide cementing substance in the healing process after inflammation. These cells resemble mast cells in the liver.

Lymphocyte: There are two kinds of lymphocytes, small and large. The latter ($10-15\mu$) has a large round nucleus with a fair amount of cytoplasm, staining blue with Romanowsky's stains, like that of Leishman's. The nucleus of the lymphocyte stains very dark, the chromatin being coarse and occurring in large masses. This variety occurs in much smaller number than the other form, namely the small lymphocyte ($7-9\mu$), which is considered to be an older form of the cell. The loss of the cytoplasm as the age of the cell advances, is thought to result in the formation of the small lymphocytes.

Functions: The formation of immune bodies which can be found in extracts of lymphocytes, suggest long range protective function against infections. Gamma globulin which is the chemical form of the immune bodies, has been detected in lymphocytes. The lymphocyte count is raised in chronic infections like tuberculosis and malaria.

Monocyte: This is the largest of the white blood cells ranging in size between 10 and 18μ . The nucleus is large, most often with an indentation on one side (kidney shaped), though this is not an invariable feature. The chromatin is very fine and the nucleus therefore is pale in appearance when stained. The cytoplasm is pale blue and clear and plentiful compared to a large lymphocyte. The functions of monocytes are not quite clear. They have been called 'macrophages' for the reason that they have been seen to remove cellular debris and dead leucocytes. It is not possible to say more than this.

Platelets: These are non-nucleated fragments of cytoplasm of irregular shape, about 2 to 3 μ in diameter and occurring in a range within 200,000 to 400,000 cells per cu. mm. In the cell matter, dark stained granules occur aggregated at the centre (chromatome), the surrounding region being pale (hyalomere) and exhibit a second type of granules sprinkled over it. The platelets are concerned with coagulation and hæmostasis. During hæmorrhage, serotonin or 5-hydroxy tryptamin is released from disintegrated platelets. This agent causes constriction of blood vessels opened out due to injury, the stoppage of bleeding facilitated by such narrowing of the injured blood vessel. Histamine is another constituent of platelets.

Thrombocytopenic purpura (see chapter on coagulation) is a condition in which increased destruction of platelets occurs. The life span of white cells and platelets is as follows:

While a circulating leucocyte may not last for more than about 10 hours, in the so called leucocyte stores or pools in the body (not exactly identified yet), they may exist for several days. The life of platelets has been estimated to be 3-5 days. Lymphocytes may have a life of as much as 3 months.

FACTORS NECESSARY FOR ERYTHROPOIESIS

These may be classified as :

- 1) Building materials
- 2) Specific stimulants
- 3) General stimulants and maturation factors.

The term erythropoiesis means the mode of formation and development of red cells. The above-mentioned factors are all necessary for an uninterrupted development of erythrocytes.

- 1) The stroma of the red cell is made up of proteins and lipids. So, for the production of red cells in adequate numbers, these building materials must be furnished in sufficient amounts in food. Iron is a component of the hæmoglobin molecule, for the synthesis of which, this element, along with first class protein, has to be taken in with food. Ferrous

salts of iron are better absorbed than ferric ones. Inorganic iron is much better assimilated than organic forms. The mode of absorption of iron, the daily requirements and other aspects of iron metabolism are dealt with in works on biochemistry, to which reference may be made.

- 2) Anoxia has been mentioned repeatedly as a specific stimulant for erythropoiesis. It is not clear as to how anoxia acts as a stimulus and the exact site of its action in the body where anoxia exerts its effect. It has been suggested that a state of anoxia may obtain in the marrow sinusoids where flow is sluggish. The higher erythrocyte count seen in subjects living at high altitudes, is ascribed to anoxia at high altitudes, causing an increase in the rate of erythrocyte production by the bone marrow. Is it to follow that the anoxia of high altitudes whips up the bone marrow to greater activity, adding to the effect of anoxia which may occur in the bone marrow even at sea level?

Erythropoietin : This is a hormonal factor of the nature of a glyco-protein, released by renal tissue and possibly by other cells, under stimulation by 'anoxia'. It is most probable that the effects of anoxia are mediated through the release of erythropoietin. This hormone, if it can be so called, seems to act on the bone marrow to bring about an accelerated erythropoiesis.

It may be that other hormones, especially one of the adenohypophysis factors, may also be involved in erythropoiesis, but it is not possible at this juncture to be more definite about this.

Early in this century, Whipple and others discovered the value of liver in diet, in the treatment of anaemia in dogs. Later, Minot and Murphy extended this observation to human pernicious anæmia patients. Castle advanced a hypothesis which accounted for the causation of anæmias of different types, as due to the lack of one or the other of the specific factors. He postulated that an unknown factor in food present in beef and liver (extrinsic factor) combined with an intrinsic factor elaborated in the stomach, to form an anti-pernicious anæmia factor, also

known as hæmatinic principle, which was absorbed in the intestines and stored in the liver. It is because of this it was held, that liver had curative properties in pernicious anæmia. The stored hæmatinic principle was drawn upon by the marrow whenever required.

The subsequent discovery of vitamin B₁₂ or cyanocobalamin, a reddish substance containing cobalt, necessitated the modification of Castle's hypothesis, as follows:

This vitamin is now identified as the extrinsic factor which is normally present in food, in association with a protein to form a vitamin protein complex. The intrinsic factor does not actually combine with vitamin B₁₂, but only brings about a break-down of the large complex into an absorbable form of vitamin by detaching a greater part of the protein molecule from the large complex. It has been subsequently found that vitamin B₁₂ is synthesised by microorganisms in the normal human intestines. The condition of pernicious anæmia results from inability to absorb vitamin B₁₂ on account of a lack of the intrinsic factor in these patients. The daily requirement of vitamin B₁₂ is about a microgram, a very tiny quantity. It has been remarked that the inability of the intestine to absorb this microscopic quantity is inexplicable, especially in view of the fact that large quantities of products of digestion of food of various kinds can be transferred across the intestinal epithelium with so much ease. The exact role of vitamin B₁₂, though not very clear, yet seems to be to control the change of the hæmocytoblast or endothelial cell to the proerythroblast stage. When there is a deficiency of vitamin B₁₂, it looks as if the hæmocytoblast is converted to a megaloblast, an abnormal cell which is seen not only in the bone marrow but also in the peripheral blood, in this condition. Vitamin B₁₂ should rightly be considered as a maturation factor.

Folic acid, known also as pteroyl—glutamic acid, is another member of the vitamin B complex group. It has the same actions as vitamin B₁₂ which it can replace as a therapeutic agent, except in one condition—in the presence of neurological symptoms accompanying pernicious anæmia (sub-acute combined degeneration). Folic acid, while it may abolish or alleviate the anæmia,

aggravates nervous symptoms. Vitamin B₁₂ does not share this disadvantage.

Vitamin B₁₂ and folic acid promote the synthesis of nucleic acids. Further details of these aspects of their action are beyond the purview of this account.

- 3) Thyroxine, one of the most potent general stimulants, is necessary for erythropoiesis. Unlike other cells in the body, the rate of multiplication of red cell precursors is so high that a lack of thyroxine will bring about anæmia. It is only in this respect thyroxine is important. It may not have any specific effect as such, on erythropoiesis. Vitamin C and probably other vitamins, may also not have any particular role in erythropoiesis. Their importance in erythropoiesis is probably only due to their usual role in metabolism in any cell.

It is not proposed to discuss the features of various forms of anæmia in this connection. While anæmia just means a reduction in the oxygen carrying capacity arising out of a fall in the hæmoglobin content of blood, a reduction in the number of red cells may be seen in certain forms of anæmia, though what really matters is the fall in hæmoglobin content. A fall in the cell count will bring about a reduction in hæmoglobin content, though in macrocytic and megalocytic anæmias, the cells, even if they are fewer in number than normally, may carry more hæmoglobin per cell which also is larger than usual, in compensation. These kinds of anæmias are attributed to a deficiency of vitamin B₁₂ or of folic acid, both of which are effective in these anæmias. In anæmias caused by iron deficiency, the cells are of smaller size than normal ones, with less hæmoglobin content. Aplastic anæmia arises out of an inability of the bone marrow to produce red cells as well as white cells. This condition may occur without any obvious underlying cause. One of the expected hazards of radiation is aplastic anæmia.

THE SPLEEN; LIFE SPAN OF RED CELLS; LYMPH AND LYMPH NODES AND OEDEMA

This is an organ hidden behind the lower ribs on the left side

and it is not palpable unless it is enlarged by as much as three times its normal size. The spleen is not absolutely indispensable for the maintenance of life. It is difficult to determine the average weight of normal spleen. Different values have been given by different workers. While the range of the weight lies between 50 to 250 gms, the most commonly occurring value is around 150 gms.

There is a thick fibrous capsule covering the spleen. While in the sub-human species, plain muscle fibres are found in the capsule, in the human spleen it is devoid of plain muscle fibres and hence it may not be susceptible to the action of adrenaline which brings about a sudden and marked reduction in the size of the spleen. The increase in the red cell count during muscular exercise, cannot therefore be accounted for in the human subject, by splenic contraction and expulsion of large numbers of red corpuscles.

The splenic artery runs into the substance of the organ at the hilus and divides again and again. The small arterial branches are each surrounded by a cuff of lymphatic tissue, giving a nodular appearance because of the varying thickness of the lymphoid tissue surrounding the vessel. The term Malpighian corpuscle is given to the collection of lymphoid cells around the arterial twigs which are found in every part of the organ. The arterial vessels lead into a network of capillaries and at the end of each of the arterial vessels, a sphincter-like arrangement of the muscle fibres is present, known as the afferent sphincter. The capillaries which are also called sinuses, are made to dilate owing to stagnation of blood in them caused by the contraction of afferent sphincter as well as the efferent spincter situated at the junction between the capillaries and venules. Outside the blood vessels, is the pulp of the spleen consisting of fibrous frame work which arises from the capsule in the form of trabeculæ, dipping deep into the substance of the organ. The pulp has a few kinds of cells, among which are large active phagocytic cells (macrophages of reticulo endothelial system) and reticulum cells and a few large so called giant cells may also be seen. It is a moot point whether blood, in its passage through splenic vessels, permeates the pulp leaving the blood vessels through apertures

in their walls. Some authors are of the opinion that blood percolates through the substance or pulp of the spleen. Others—like Knisely, do not concur with this.

Function of the spleen: A) Production of Lymphocytes—The generation of lymphocytes takes place at the centres of the lymphoid aggregations which are pale staining and known as the germinal centres.

B) Storage of blood—In view of the sluggish flow of blood through the splenic substance, the spleen in lower animals is taken to function as a store house for erythrocytes which can be liberated into the general circulation, under emergency conditions. As pointed out already, the human spleen may not serve such a purpose.

C) Destruction of RBCs; The spleen seems to render the RBCs stored in it, vulnerable to hæmolysis. Such cells hæmolyse at higher salt concentrations than normally. Splenectomy makes red cells less susceptible to hypotonicity of saline. The presence of iron-free pigment as well as pieces of red cells in the cells of spleen, indicates the destructive functions of the spleen as regards red cells.

D) Destruction of platelets—It is possibly the function of spleen.

E) Formation of antibodies—This may be related to the production of lymphocytes. The spleen is also the site of formation of bile pigments because of the presence of reticulo—endothelial cells.

Life span of Red cells: The average life of a red cell is about 120 days in the circulation. This estimate has been made possible by observing red cells whose hæmoglobin has been tagged with radioactive iron. Senile red cells are destroyed in one of three ways:

1) It is possible that there are circulating hæmolysins which break up worn out red cells.

- 2) The life of a red cell may also come to an end by the action of macrophages of R. E. system which engulf damaged red cells.
- 3) The most probable means by which destruction of red cells is achieved to the largest extent, is by the so called wear and tear to which they are subjected as they move in the blood vessels. Every time the ventricle contracts, red cells are hurled into the blood vessels at a high velocity against other red cells. Also in the capillaries, cells undergo distortion as they traverse these vessels which are narrower than themselves. Wherever blood vessels branch, some cells are saddle-bagged—they are made to impinge at the point of division in a blood vessel so that they get folded against the point of bifurcation. Repeated mechanical insults like this gradually wears out the cells and they get lysed.

Lymph and Lymph nodes: Lymphatic vessels are very delicate and formed of an endothelial lining with a fibrous outer covering. A few muscle fibres are present in larger vessels and valves are also seen. The contractions of skeletal muscles and the thoracic respiratory movements help in the flow of lymph. The thoracic duct is the main lymphatic vessel and it drains lymph from the whole of the body, excepting the right upper half of it which is drained by the right lymphatic duct. Both these vessels join the great veins at the root of the neck and valves are present at the junction.

The lymph nodes: A typical lymph node shows the following features: Several afferent lymph vessels enter the node, the entrance being guarded by valves. The lymph flowing into the node spreads along the subcapsular spaces guarded by trabeculae, through the pale staining cortex and thence into the medulla. The lymph is collected from the node by a single efferent vessel.

Composition of Lymph: Lymph resembles tissue fluid and has a composition similar to plasma, though with much less protein—0.5 to 0.7%. Albumin : globulin ratio is much higher in lymph than in plasma. Very little prothrombin is present in lymph. The red cells are very few in number but lymphocytes

may occur in numbers ranging between 1000 to 20,000. Normally, lymph is light yellow in colour, but during absorptive phase it may be milky owing to the presence of chylomicrons.

Formation of Lymph: The conditions increasing the formation of tissue fluid also facilitate the formation of lymph. Lymph capillaries are more permeable than blood capillaries and their walls offer no barrier to the passage of crystalloids and even proteins.

Conditions increasing lymph flow :

- 1) Increased capillary pressure as in venous obstruction.
- 2) Increased permeability of the capillary walls—*a)* due to rise in temperature. *b)* capillary poisons—lymphagogues of the first order. (peptones, histamine, foreign proteins, liver extract). *c)* anoxia.
- 3) Hypertonic solutions of glucose, sodium sulphate etc. used in dressing wounds. Lymphagogues of second class.
- 4) Increased functional activity of a part of the body.
- 5) Massage and passive movement of the body causing increased blood flow.

Oedema: Accumulation of fluid in extracellular spaces caused by—

- 1) Reduction in osmotic pressure of plasma.
- 2) General or localised increase in capillary pressure due to venous stasis.
- 3) Increased permeability of capillary membranes as in anoxia.
- 4) Obstruction of lymph channels.

Examples of oedematous condition: congestive cardiac failure, nephritis, inflammations, giant oedema, elephantiasis, burns, and anæmia.

RETICULO-ENDOTHELIAL SYSTEM

The neutrophils of blood have the phagocytic property and consequently they ingest bacteria and small particles of foreign matter. These cells are referred to as microphagocytes. There are larger cells known as macrophagocytes whose representatives in blood are the monocytes and in solid tissues the so called histiocytes. In addition, there are other cells which exhibit similar properties. All these are members of the reticulo-endothelial system. The term, 'endothelial' however, is not appropriate, as they are mesenchymal phagocytes. Because of their avidity for certain stains like pyrrol blue, their presence in tissues can be detected by injecting (in animals) weak solutions of these stains and later examining the tissues under the microscope. Pyrrol cells is another term used to refer to the family of these cells which are said to be vitally or supravitaly stained.

Reticulo-endothelial cells are broadly divided into fixed and wandering types. The accompanying scheme on page 67 shows the different kinds.

An infection or inflammation in any part of the body transforms the resting cells into wandering cells. When the stimulus provoking their movement ceases, they once again come to rest in some part of the body or the other.

Functions of the reticulo-endothelial cells :

1. As mentioned in the beginning, by virtue of phagocytosis they remove dead and effete cells and aid in repair processes as after inflammation.
2. These cells are responsible for the degradation of the hæmoglobin molecule and the formation of bile pigments.
3. They may also be involved in the development of antibodies.

Radio-opaque substances like thorotrast are taken up by reticulo-endothelial cells in the various viscera. Consequently, it is possible to visualise by means of X-rays, the outlines of various inner organs like the liver, spleen and the kidney.

Reticulo-endothelial cells

Resting cells (fixed cells)

a.

In connective tissues or serous membranes (resting wandering cells)

b

Reticular cells in reticulum of spleen, lymph nodes & bone marrow.

c

Endothelial cells lining the sinuses or capillaries of liver (Kupffer cells), spleen, bone marrow, adrenal gland & pituitary.

d

Microglia.

solid tissues,

Blood histiocytes.

Wandering cells

e

f

1

2

of extraneous monocytes origin

CONTRACTILE TISSUE

This term refers mainly to muscle tissue of three well differentiated types and also certain star-shaped cells—the myoepithelial cells—which are found in the walls of the alveoli and ducts in the breast. Muscle tissue, by virtue of its contractility, is responsible for movement or locomotion.

The three varieties of muscles are: 1) Plain or unstriated muscle commonly known as involuntary muscle. 2) Cardiac muscle which shows striations, both transverse and longitudinal (in the muscle fibres) and certain features like branching of the muscle fibres not found in striated (or striped) muscle. 3) Striated or striped muscle which is also called skeletal or voluntary muscle.

THE STRIATED MUSCLE

The striated muscle will be described first in view of its role in the movement of the body and the limbs. The other two types will be referred to subsequently and also a comparison will be made of the three, regarding structural and functional aspects.

Striated muscle or striped muscle is so called not because of the presence of longitudinal striations which are seen even in the so called plain or unstriated muscle, but on account of the transverse markings which occur both in the striated as well as in the cardiac muscles. The alternative terms, skeletal muscle and voluntary muscle, fall short of being ideal and do not satisfy all the requirements. The tongue, though voluntary and striated, is not a skeletal muscle as it has mostly no skeletal attachment as such. All striated muscles (cardiac muscle not included in this instance) contract reflexly also, though they have been for a long time considered to be only under voluntary or volitional control. Also as Wilkie puts it, it is not known, except in the case of man, whether the striped muscles of lower animals like the frog, are activated voluntarily or not. He proposes the name 'executive

muscle' to replace the older terms, if it is necessary to designate it at all by a special name. It is pertinent to say that the involuntary muscle (plain or unstriated and even cardiac) is, in the case of exceptional individuals, under volitional control. Some subjects can change their heart rate at will. Contrarily, striated muscles of larynx, pharynx and upper œsophagus are not under voluntary control. The terms 'voluntary' and 'involuntary' are archaic and should be discarded.

Striated muscles are of various shapes and sizes. Some are of large bulk, like the gluteus maximus and the quadriceps femoris. Others are very tiny, like the stapedius. They have also been classified according to form, into quadrilateral, fusiform, strap-like, unipennate, bi or multipennate etc., according to the relationship between the direction of fibres and the line of pull of the muscle. Each muscle consists of a very large number of muscle fibres, all of which are enclosed in a connective tissue covering, the epimysium. A number of bundles of muscle fibres exists in each muscle mass and each is again covered by a layer of connective tissue, the perimysium. Each individual muscle fibre has an extraneous covering of endomysium in addition to the sarcolemma, a tough double-layered membrane (100 Å thick) which is the outermost structure of the muscle fibre and part of it. It is poorly stained and is seen best at points where a muscle fibre has been broken while teasing. A single striated muscle fibre is more or less cylindrical and is of great length compared to its thickness. This is as it should be, since contraction of a muscle should result in appreciable shortening so as to effect a movement at a joint. A muscle fibre may range from 1 to 120 mm in length and between 10 and 100 μ (fig 1A) in thickness. Inside the sarcolemma is the sarcoplasm, a fluid like matrix, in which are suspended the myofibrils. The sarcoplasm contains electrolytes like potassium, magnesium and phosphates and enzymes. A number of granular bodies, the sarcosomes exist in between the myofibrils. These are said to be similar in function to mitochondria of other cells. Probably, in the mammalian muscle, the larger sarcosomes (the mitochondria) are concerned with oxidative metabolism with production of ATP. Most of the granules are confined to the I segment (see below) in close proximity to the A band, so as to ensure efficient delivery of ATP. Glycogen is said

to exist in the sarcoplasm (free form) and also in the protein-fixed state, attached to the myofibrils.

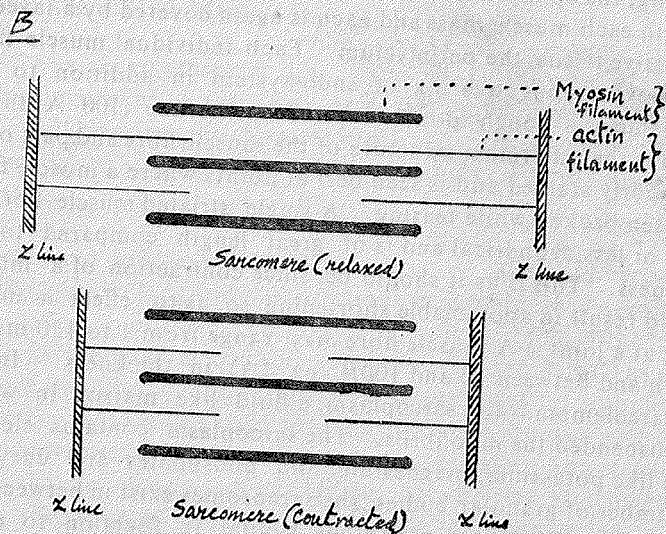
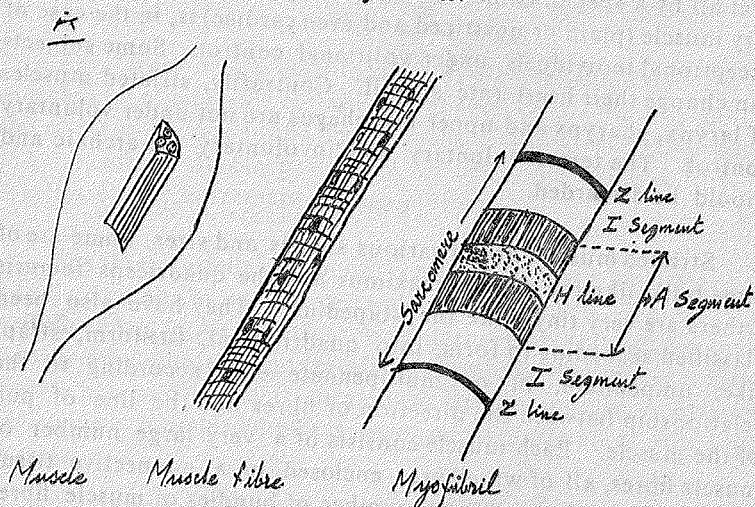


FIG. 1

In the I band on either of the Z line, ill-defined fibrous structures are seen in the sarcoplasm. These are apparently attached to the myofibril. Formerly, these were known collectively as

sarcoplasmic reticulum. According to older views, they were concerned with protein synthesis.

The protein myoglobin is found in a dilute strength in the sarcoplasm. It is thought to be a store for oxygen (like HbO_2), to be utilised by the cytochrome system in the mitochondria. Lodged just inner to the sarcolemma, at intervals along the length of the muscle fibre, are a number of nuclei. They lie outer to the myofibrils. The exact mode of linking between the contractile portion of a muscle—the muscle fibres proper with the tendon fibres (the non-contractile elements)—awaits further study.

Myofibrils: The sarcoplasm surrounds individually, a large number of bundles of myofibrils, as well as all of them together. The longitudinal striations of a muscle fibre are due to these myofibrils. In a transverse section, the bundles appear as circumscribed areas (Conheim's fields) with the cross sections of myofibrils seen in each area, which is known as a Conheim field. Each of these myofibrils is only a fraction of a micron in thickness and in turn, each consists of a number of parallel myofilaments or protein threads mainly of actin and myosin.

Many fundamental investigations have been carried out to unravel the ultra microscopic structure of the myofibril. When an unstained single muscle fibre is looked at under the ordinary light microscope, no details are seen. They appear to be transparent tubes. With the use of iron-hæmatoxylin as a stain, the muscle fibre is seen to consist of alternate light and dark bands (cross striations) running throughout the thickness of the fibre and when viewed at an angle, the fibre looks like a pile of dark and light discs alternating with each other. This appearance is better appreciated at the edges of the fibre than in the middle portions. The dark regions were known as A bands (anisotropic) and the light ones as I bands (isotropic). The term anisotropic meant that the refractive index was not the same in different directions. In one direction it was least and in a direction perpendicular to the first one it was greatest. Isotropism signified uniform refractive index in all directions. The anisotropic portions had also, in general, a higher refractive index than the isotropic ones. When an unstained muscle fibre is examined

under a polarising microscope, the arrangement of alternating light and dark discs can be seen, but which disc appears dark and which light, depends on the setting of the microscope. A phase contrast microscope also enables the same details to be seen.

In order to make out finer details, the muscle fibre has to be broken up into its constituent myofibrils so that one of these can be examined separately. Under an interference microscope, the myofibril was seen to be made up of a number of sarcomeres (about $2\text{--}3\mu$ in length), each bounded at either end by a dark thick line (Z line or disc) and inside were seen two lighter portions, one at either end, the I half segments or bands and a middle dark region, the A segment. Also a lighter area, the H line, was seen bisecting the A segment (Fig. 1A). The I band (2 halves together) measured 1μ and the A band 1.5μ in the sarcomere of length 2.5μ .

A. F. Huxley and Neidergerke established by the use of an interference microscope in the examination of a living muscle fibre, that both when the sarcomere was stretched and during contraction, it was only the I band that showed increase and shortening, respectively. The A segment did not change in length appreciably, except with extreme degrees of contraction, at which the A zone formed a contraction band along with the Z line which also formed a fainter contraction band.

Hanson and H. E. Huxley studied individual myofibrils got from a glycerol-extracted muscle. Under a phase contrast microscope which was set to show the A bands as dark regions, these were found not to elongate or contract at moderate degrees of contraction. However, contraction bands in the A segment were seen when the myofibril was made to shorten to a very small length. The same workers (H. & H. E. H.) selectively extracted the proteins, myosin, actin and probably tropomyosin, in successive stages. It was shown that myosin was confined to the A band and, actin and tropomyosin to the I band. When the three proteins were removed, still the structural integrity of the sarcomere was not disrupted because of the stroma proteins; the Z lines were also left intact and in position.

The next stage in the unravelling of the ultrastructure of the myofibril came about from the work of the same two pairs of authors named above. A. F. Huxley and Neidergerke conducted X-ray diffraction studies of the living muscle, while the other two authors made dehydrated and fixed preparations of the myofibril to be looked at under the electron microscope. The two sets of investigations led to complementary results, according to which the sarcomere consists of two sets of myofilaments—actin and myosin—running parallel to the length of the muscle fibre. In the I segment (Fig. 1B), only actin (thin- $40\text{\AA}$) filaments were seen. These consisted of two actin molecules spirally wound around each other. In the two end portions of the A segment, both actin and myosin (thick- $110\text{\AA}$) filaments occur, each of the latter surrounded by six of the former at a distance of $450\text{\AA}$ and arranged hexagonally. Tropomyosin probably is present along with actin. In the H zone of the A band, only myosin threads are present. Myosin molecules seem to be arranged as a series of lateral projections from the core or trunk of the filament.

THE INTERNAL CONDUCTING SYSTEM OF THE MYOFIBRIL

- I. The Z line which runs from one fibril to the next was shown to be concerned in some way with the activation of the interior of the muscle fibre, as was shown by A. F. Huxley. When a very fine electrode was placed so that its tip was in contact with the Z line region of a muscle fibre and electric current was passed into the fibre, a localised contraction of the half sarcomeres on the two sides of the Z line took place. On the contrary, if the electrode was placed on the fibre midway between two adjacent Z lines, no change occurred even when stronger current was passed in. The Z line was taken to provide a conduction system between the exterior and the interior of the fibre and was responsible for linking excitation with the contraction process.
- II. Reference has already been made to the sarcoplasmic reticulum which is very markedly developed in rapidly contracting muscles. This consists of two kinds of tubular systems. One is formed of the transverse or T-tubules, running from

one side of the muscle fibre to the other and containing extracellular fluid. The longitudinal system consists of short tubules running in a direction parallel to that of the sarcomere. Each tubule has a bulbous termination which abuts the T-tubule (running transversely), on the other side of which there is another bulbous ending, belonging to another longitudinal tubule. Two such wide terminations (cisterns) with a T-tubule in between, is called a triad. The T-tubule which runs inwards along the Z line is thought to convey the action potential or depolarisation process (local circuit) which is conveyed by the sarcolemma (along the length of the muscle fibre) to the interior of the fibre so as to activate all the inner myofibrils. The longitudinal tubules serve as return channels for local currents which enter them at the region of the triad and pass out through the sarcoplasm and the sarcolemma, back to the exterior. Huxley's findings can be explained by the fact that the T-tubules run inwards along the Z lines and so the Z line region when excited, gives rise to contraction of the neighbouring half sarcomeres.

Chemical constituents of muscle: Three fourths by weight of muscle is water. Of the remainder, a fifth is made up of various substances like glycogen, and extractives (creatine, creatine phosphate, adenosine phosphate, lactic acid, carnosine, anserine etc.). Half of the proteins (these constitute $1/5$ th of the weight of the muscle) of the muscle consists of actin and myosin, the contractile proteins. The other proteins are tropomyosin, albumin, stroma protein, globulin, myoglobin and cytochrome pigments. The last two are concerned with the supply and utilisation of oxygen for furnishing the energy requirements of the muscle fibre. Adenosine triphosphate (ATP) and creatine phosphate (CP, Phosphagen) are substances which yield energy for contraction, when a phosphate radicle is split off from each of them. Myosin is a fibrous protein (M. W. 450,000). In solutions, it shows flow birefringence. It was found that myosin could bring about the breakdown of ATP into ADP and phosphate, by an enzymatic action. Ionic calcium activates the reaction while magnesium inhibits it.

Actin is of molecular weight 70,000 and occurs in two forms. The G actin or Globular type is the basic unit. In the presence

of salt, G actin polymerises end to end and forms the fibrous or F actin which is the form seen in the muscle.

Actomyosin which results from a mixture of actin and myosin solutions, has a stronger action on ATP than myosin itself. This complex substance forms a very viscous solution. When ATP is added to actomyosin in solution which also has KCl in a certain concentration, the two proteins dissociate and this is followed by the breakdown of ATP itself. Szent-Gyorgyi made a remarkable discovery that actomyosin threads could be made to shorten on being immersed in ATP solutions and further, that muscle fibres preserved in glycerol at cold temperatures became electrically inexcitable though they could contract when placed in ATP solutions. Such fibres as are treated with glycerol are set at a shortened length after they are exposed to ATP (in solution) and later washed free of the ATP. When however such (shortened and fixed) fibres are next put in ATP solution to which mersalyl, a mercury compound (diuretic), has been previously added, the fibres actually 'relax' to their original length. This action of ATP is known as the plasticizing action and is responsible for passive relaxation of muscle fibres. Physiologically, it is surmised that at rest, the ATP splitting action of myosin is suppressed and so ATP has a plasticizing action on the muscle fibres. The antagonistic effects of Ca^{++} and Mg^{++} are just balanced one against the other. On stimulation of the muscles, the balance is upset in favour of calcium ions, in some inexplicable way and ATP breaks down, liberating the energy for contraction. Interdigitation or sliding of the actin filaments into the spaces between the myosin filaments takes place, causing a shortening of the sarcomeres and hence of the muscle fibre. When ATP is resynthesised, it exerts its plasticizing action and causes the muscle fibre to relax. Szent-Gyorgyi was awarded the Nobel prize for his work on the muscle.

The actual sources of energy for muscle contraction; Several workers (Krebs and others) tried in vain to demonstrate the diminution in the ATP stores consequent on a single twitch. It seemed possible that ATP, even though it may break down during a twitch, was very rapidly resynthesised, thus making it impossible to detect the change.

Muscle glycogen was shown to be reduced in amount when a muscle was repeatedly excited under anærobic conditions and lactic acid was produced. When such a muscle was exposed to oxygen, lactic acid content was diminished and the glycogen was restored to some extent. This showed that glycogen was the ultimate source of energy for contraction.

A crucial experiment was performed by Lundsgaard in 1930. A muscle was poisoned with iodo-acetate which suppressed the formation of lactic acid during muscle contraction. The muscular tension produced was quantitatively related to the diminution in the muscle content of phosphocreatine, discovered earlier and independently by the Eggletons in Britain and Fiske and Subba Row in the States. The involvement of creatine phosphate in muscular contraction, was shown by this work.

It was subsequently deduced that it was creatine phosphate, by its break down, that yielded phosphate for the resynthesis of ATP from ADP.

Thus, ATP by its break down, furnishes the energy for contraction, as a first step. It is quickly restored by the transfer of phosphate from creatine phosphate in the muscle. This mode of restoration of ATP is restricted by the limited stores of creatine phosphate in the muscle.

The breakdown of blood glucose and muscle glycogen to yield pyruvate aerobically or lactic acid anærobically, furnishes chemical energy to restore ATP. The final oxidation of pyruvic acid to carbon-dioxide and water through the Krebs's cycle and the cytochrome system, brings about the yield of more ATP molecules. In the absence of oxygen, lactic acid accumulates in the muscle during contraction and soon puts a stop to further muscular activity due to the fall in pH, as happens in severe exercise. In moderate exercise, the supply of oxygen keeps pace with the formation of pyruvic acid (which in turn is oxidised to carbon dioxide and water) and the breakdown of ATP, so that the resynthesis of ATP is fast enough to make continued muscular effort possible. Fatty acids and even acetoacetate furnish energy

by their oxidation. This is so in the case of the heart muscle even ordinarily, for its activity. Resting skeletal muscle derives its metabolic energy from these non-carbohydrate sources. But during contraction, skeletal muscle preferentially uses carbohydrates. More details regarding these chemical changes will be found in works on Biochemistry.

The sliding filament hypothesis: The essentials of this postulation are that during muscle contraction, the actin filaments do not crumple up but merely slide into the A segment, into the spaces between the myosin threads (fig. 1B), maintaining their spatial relationship with the latter. Only under extreme degrees of shortening, folding up of protein filaments may occur. The actual mechanism by which the actin threads move or slide into the A segment is still incompletely understood.

This was sought to be explained by A. F. Huxley on the basis of side links or cross bridges projecting outwards from the myosin threads and running towards the actin filaments. These linkages occur at regular intervals (of $435 \text{ \AA}$) on the myosin filaments, six at each site and each one directed towards one actin thread which has a 'reactive site' to make contact with one cross bridge. Certain possibilities as regards the actual mechanism of the sliding movement have been advanced in the light of the physical and chemical properties of the contractile proteins.

According to one view (not Huxley's), the actin filaments possess negative charges at the reactive sites. The cross bridges of myosin which have ATP molecules in close association with them are also negatively charged and thus, a repulsion between actin and myosin exists. The absence of ionic calcium at this time (during the resting state of the muscle) helps to maintain this condition of separation between the two proteins. On excitation, free calcium ions (with positive charges) are liberated and these, by attaching themselves to the side links of myosin and the reactive sites of actin because of their negative charges, bring about linking of the two protein filaments by means of the cross bridges as well as the sliding of actin threads past those of myosin. Calcium also activates the myosin to take the role of ATPase whereby the ATP attaching itself to myosin is split.

Tropomyosin which is an integral part of actin filaments normally (at rest), keeps actin and myosin separated. It is probable that other muscle proteins may also play a role in this mechanism.

A. F. Huxley's concept was based on a ratchet device in the promotion of the sliding movement. At rest, the cross bridges bearing negative charges are themselves repelled from the main myosin thread which also is negatively charged and so the bridges stand outwards from the myosin. The ATP molecules, in association with the cross bridges, also bear negative reactive points or sites and these are also repelled by myosin. But in the presence of calcium ions, the cross bridges bind the two protein filaments together, as described above. In this process however, since the negative charge on the cross bridge is neutralised, it is drawn nearer the myosin thread and consequently, as an effect of the component of this force resolved in the direction of the actin filament, the actin is drawn 'one step' inwards into the A segment. But now the ATP molecules on the cross bridges come closer to myosin spatially and are split by the ATPase action of the protein. The calcium-linked cross bridges between the two protein filaments are now broken and the actin filament, in the meanwhile, has moved over the distance between two adjacent bonds. The events described are repeated and during every cycle, the actin thread moves further inwards and thus, 'contraction' occurs. Every time ATP is broken down, it is reconstituted either by obtaining energy from creatine phosphate or deriving it from glycolysis.

An alternative mechanism known as the Solenoid theory has been postulated. This is based not on the bonds between the two protein filaments but on electrostatic forces between the two, which can be effective even over relatively great distances (compared to the size of calcium ions) in the sarcomere. It takes into consideration the finding that, in contraction the myofibril swells up and the interfibrillar distances increase. The movement of the actin filament is assumed to be due to a vector or component of the electrostatic force of attraction pulling on the end of the actin filament.

A few mechanical aspects of muscular contraction are now briefly discussed:

From studies on the sarcomere relating the tension produced (by contraction) to the length, it has been observed that the maximum tension is seen when the sarcomere is at such a length that the actin filaments overlap all the cross bridges of myosin. This has been seen in the whole muscle also. The tension developed in contraction is maximum when the muscle is at its 'normal stretched' length. *A muscle is said to contract isotonically when its tension remains constant as the muscle fibres shorten. Isometric contraction occurs if the tension rises with no or minimal shortening of the fibres.*

On stimulation, a muscle does not show shortening at once. There is a short delay during which the force exerted by the muscle fibres brings about the stretching of certain structural elements in the muscle, all of which form the series elastic component, formerly considered to reside in the tendon only, but now known to be present in the active contractile elements and also associated with the Z lines. In addition, a parallel elastic component is present and is represented by the connective tissue and sarcolemma. This is responsible for withstanding tension as well as for latency relaxation (see below).

The Active State: This is represented by an increase in the resistance to stretch, which results from excitation of the muscle. It is measured in terms of the isometric tension developed in the muscle. On excitation of the muscle and after a short latency, the shortening progresses rapidly and at a maximum rate to reach its full intensity which is maintained for a time and then declines rapidly. The duration over which the active state lasts, is dependent on temperature. At higher temperatures, duration is shorter. Further, it has been found that the time course of the active state in a twitch, coincides exactly, in the rising phase, with that in a tetanus. The two cases differ in that, the active state declines rapidly in the twitch while it is more prolonged in a tetanus.

The heat production in a contracting muscle was studied notably by A. V. Hill who won the Nobel award for this single

piece of work. He used a thermopile, specially constructed for him by an able and competent technician, A. C. Downing. It consisted of a series of thermocouples formed of copper and constantin (copper 60% and nickel 40%) junctions. The recording device was a sensitive galvanometer with a short period of oscillation. The muscle, actually a pair of frog's sartorius muscles, was placed in contact with every alternate junction of the thermopile which was heated by the muscle and thereby produced a current which was recorded by the galvanometer, enabling measurements. The time course of heat production was very short and the individual fluctuations were very rapid. Hill observed the different and successive phases of muscle heat production in both muscle twitch and tetanus. Muscle heat was broadly divided by him into the following components:

- 1) Initial heat — that which is produced during contraction due to breakdown of ATP and phosphagen (CP).
- 2) Delayed heat — a) anærobic heat — which is produced in relaxation and afterwards, on account of the breakdown of glycogen to lactic acid in excess of what (derived from the same source) has been utilised for resynthesis of CP and ATP.
 b) Delayed ærobic heat—On admitting oxygen, it is utilised to oxidise part of the lactic acid completely to carbon-dioxide and water. This results in release of energy, part of which is utilised to reconvert the remaining lactic acid to glycogen. The remainder of the energy is wasted as heat which is the delayed ærobic heat.

Later, with further analysis of heat production in a single isotonic twitch—i. e. — a contraction in which all the fibres of a muscle take part, though the duration is very short—a few hundredths of a second — the heat production was described as under:

- 1) Heat of activation: This appears very soon (even before actual shortening) after excitation and declines as contraction proceeds. It is always constant and independent of any factor.

- 2) **Heat of shortening:** This coincides with the contraction of the muscle and is dependent on the rate of shortening or on the tension developed.

No heat is evolved in relaxation, except what is derived from the degradation of mechanical energy into heat. When a muscle contracts isometrically, all the energy released is expended or wasted as heat. If work is performed by a muscle, as it shortens, about 20 to 25% (upto 30%) of the energy output is rendered useful in performing work. The mechanical efficiency of a muscle is maximum when it contracts at about 30% of its maximum velocity. The muscle is much more efficient as an engine than the steam locomotive with only 7-20% efficiency.

Heat of Tetanus: When a muscle contracts (isometrically) tetanically in an atmosphere of nitrogen, heat is produced in four stages.

- | | | |
|--|---|-------------------|
| a) a large and quick output of heat in the beginning of contraction | } | Contraction heat. |
| b) A maintained heat production during contraction (tetanus) | | |
| c) A small amount of heat released during relaxation—relaxation heat. | | |
| a), b) and c) together comprise initial heat. (b) is almost absent in a twitch. | | |
| d) A quantity of heat is slowly liberated after relaxation is over and is continued for quite some more time. This is the delayed anærobic heat. | | |

The heat produced (as described in a, b, c and d) when a tetanus occurs in nitrogen, is less than what is given off when oxygen is admitted. In the latter case, the output of heat is 2.2 times that the former (as shown below) because of the addition of oxidative heat. The delayed anærobic heat and the oxidative heat will together constitute recovery heat, distinct from initial heat.

The entire output of heat of contraction is summed up schematically:

A. *Initial heat*

	<i>Proportion of total</i>
1. Contraction heat	0.65
2. Relaxation heat	0.35
	—
(Total)	1.00

B. *Recovery heat* (figures indicate quantities of heat in the same proportion as in initial heat).

1. Delayed anærobic heat—net heat released after the requirements for CP synthesis are met with—	0.08
2. Oxidative heat — net release of heat after restitutive processes (glycogen re-synthesis) are completed	1.16
	—

Total 2.24

Rigor Mortis: This is otherwise known as post-mortem rigidity or stiffening of muscles after death. Its onset may be from 10 minutes to 6 hours after death, the exact time depending, among other factors like external temperature etc., on the mode of death. In deaths arising out of physical violence, when the victim offers stiff resistance, rigor comes on very fast. So it is, in hunted animals. It disappears in about 24–36 hours. These facts are of medico-legal importance in enabling the pathologist to determine the time of death. Rigor commences in the head and neck muscles and spreads to the upper limbs next and finally to the lower limbs. It also disappears in the same order. The disappearance of rigor gradually, is on account of autolysis (by muscle enzymes) of coagulated muscle proteins. The muscles in rigor show certain characteristic changes.

1. Shortening of muscles with development of opacity.
2. Heat is evolved from the muscles and carbon dioxide is given off. Lactic acid is produced.
3. ATP stores are depleted completely. This is prevented by iodoacetate. The exhaustion of ATP renders the 'bondage' between actin and myosin permanent and prevents the relaxation of the sarcomere.

Types of contraction of a striped muscle : It has already been mentioned that a muscle can contract either isotonicly (without change in tone) or isometrically (without diminution in length). The single twitch of a muscle is an experimental phenomenon. Under ordinary living conditions, all the nerve fibres to a muscle are not excited and so all the motor units (a spinal motoneurone along with the muscle fibres it innervates) in a muscle are not thrown into activity together. However, in the laboratory, a simple muscle twitch which results from the stimulation of all the fibres of a motor nerve, is a convenient type of muscle activity intended for study of muscular contraction. A mammalian muscle loses its excitability very soon after its isolation from the rest of the body unless its blood supply is ensured. Though Sherrington and others have studied muscle performance in the dog and cat, yet for elementary laboratory experiments on the muscle, the frog or toad muscle, not being a very choosy kind of tissue, is the most convenient one to work with. As Wilkie opined, since much of the physiology of skeletal muscle is yet to be unravelled, fundamental advances even in the case of frog muscle will be worthwhile and should not be looked down upon.

A motor unit may be small or large depending on the importance of the muscle in the body. Those which are capable of executing fine and precise or skilled movements have small motor units, eg.—finger muscles—in which each neurone innervates a few muscle fibres only. Those which bring about gross or coarse movements like the gluteus maximus or the quadriceps femoris, have very large motor units, each comprising of a large number (upto a few hundreds) of muscle fibres. In voluntary or willed movements, not all the units in a muscle are active at the

same time. Even though all such movements last for appreciable durations of time, yet all units are not engaged simultaneously. They act in relays — In the beginning only a few come into play and as they cease their activity, others in increasing numbers become active. Towards the end, most have become inactive and only very few are still under excitation, these becoming active lastly. In other words, there is asynchronous activation of the units. Nevertheless, the movement is smooth (not twitchy or jerky) and sustained and is hence called an asynchronous tetanus. In the laboratory, when the motor nerve is stimulated by a rapid succession of stimuli (at a rate greater than 30/sec for a frog's muscle), a synchronous tetanus results. The rate is very high for mammalian muscles. All the motor units are excited together, giving rise to a smooth sustained contraction (tetanus). But this is a highly artificial type of muscular activity, not seen in the muscle in situ in voluntary movements. The smoothness of such a movement (tetanus) is only an apparent effect. If the electrical activity of the contracting muscle (electromyogram) is studied, it will show a spike potential for each stimulus applied, however fast the rate of stimulation may be. There is no mixing or merging of the electrical signals. What has really happened is that the muscle in tetanus is not allowed to relax sufficiently after one contraction (due to a stimulus) before another follows (due to the next stimulus). This apparent effect, as seen in graphic records or on visual inspection of the muscle, is referred to as Wave Summation.

When the stimulus to a motor nerve (in a muscle nerve preparation) is increased in strength continuously (not in steps), it is found that the rise in tension produced by the muscle does not rise continuously, but in steps. When the strength of the stimulus is at a minimum, only a certain number of motor units will be active. Until the stimulus strength exceeds this by a certain margin, more units will not be activated. Even after that, there will be many more to come into action. That is to say that there are several groups of motor units whose thresholds for stimulation vary. Some have very high excitability (low thresholds) and some have low excitability (very high thresholds). In between the lowest and the highest limits, there are several groups, each with a different threshold. Starting with the group with the

lowest threshold, the next group will be thrown into activity only when the stimulus strength approaches the particular threshold and not before. This is so also for the other groups with higher and higher thresholds. This kind of adding on in groups, of active motor units, to those already in action when the stimulus is gradually raised in strength, is termed 'Quantal Summation', in contrast with 'wave summation' (see above). Other types of summation are described in the sections on properties of cardiac muscle and properties of spinal reflexes. The allied phenomenon of recruitment of motor units is referred to under spinal reflexes. It is useful to remember that the "all or none law" does not hold good in the case of a whole skeletal muscle (unlike the heart). However, it is valid with regard to the single skeletal muscle fibre and even so it is because of the muscle fibre membrane which bestows the all or none character on the fibre. The actual contractile mechanisms bereft of the coverings or conduction systems do not conform to this law.

When the rate of stimulation of a motor nerve is not high enough to effect complete fusion of the individual contractions, a partial or incomplete tetanus (clonus) results. This is seen clinically as an effect of upper motor neurone lesion.

It is a very familiar exercise for students to record a simple (isotonic) twitch of a frog's muscle and study its time relationships. When a single induction shock is applied to the nerve, an impulse is generated and it is conveyed to the muscle whereupon a twitch occurs. There is a time lag (latent period) between the moment of application of the stimulus and the onset of contraction. This is accounted for by 1) time taken by the impulse to reach the muscle end plates, 2) the end plate or synaptic delay, 3) true latency during which the electrical impulse is generated and conducted along the muscle fibres, 4) latency relaxation, 5) rigidity and inertia of the recording system. The latency relaxation is attributed to the stretching of the parallel elastic component. The actual shortening follows this phase. The muscle shows, almost concurrently with the appearance of latency relaxation, an increase in its transparency to light which is reversed as the muscle shortens. The latent period in the frog's muscle nerve preparation is about 0.01 second. On an average, the three

phases — latent (0.01), contraction (0.04), and relaxation (0.05) periods all sum up to about 0.10 sec. When the temperature of the muscle is raised as by immersion in warm saline in a Lucas' trough, all the phases are shortened and when the muscle is cooled, the three phases are lengthened. Raising the temperature by 10°C shortens the latent period by a factor of about 2.1 (Q10). Muscle is irreversibly damaged at temperatures between 40°C and 45°C .

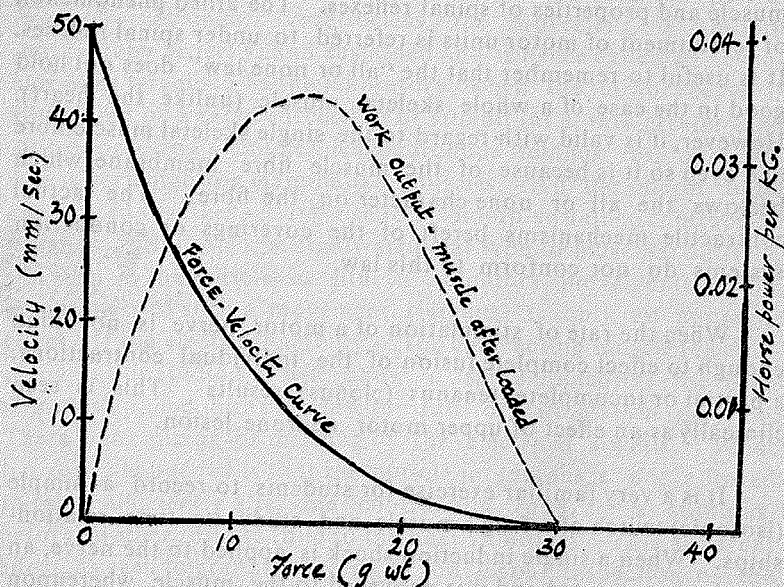


Fig. 2. Force-Velocity Curve

Force-Velocity curve: The relationship between the force exerted (weight attached) on a muscle opposing shortening (isotonically) and the velocity of contraction (slope or the 'tangent' at the rising phase of the twitch record) has a characteristic shape. The curve (Fig. 2) starts from a point of the Y-axis (at a certain distance above the point of origin) and declines curvilinearly (with convexity towards the origin) and meets the X-axis at a point (at a certain distance from 0). An algebraic equation was derived by A. V. Hill to fit this experimental curve. While other equations could equally be made to

fit the same curve, Hill's equation had a special merit in that it conformed to the measurements of heat produced during contraction.

If the muscle is not stretched by the weight attached, prior to its shortening, the muscle is said to be after-loaded. The work done by the muscle in raising each weight suspended from it can be calculated and if a graph be constructed depicting the variation of work output of the muscle with changes in the weight used for after-loading the muscle, it has the shape of an inverted parabola. That is to say that when the weights are increased, starting with a small one, the work performed shows an increase till a maxi-

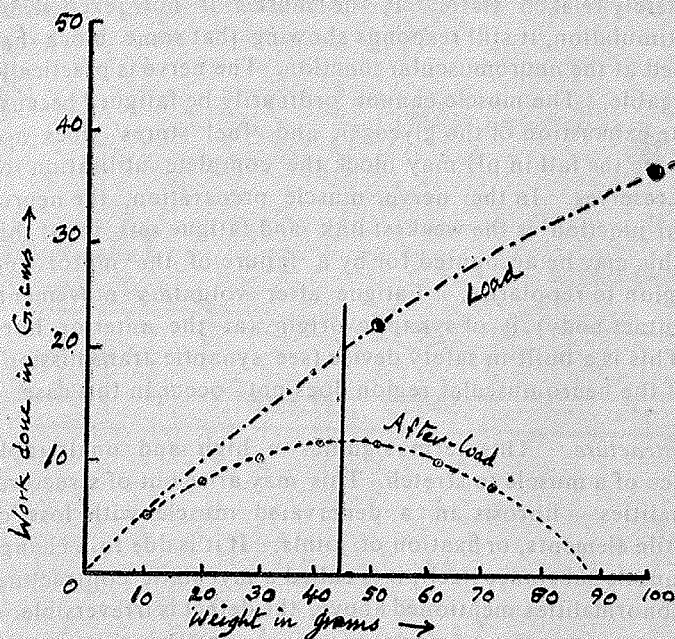


Fig 3. Work Output of muscle

mum is attained. Further additions of weight brings down the output of work. This shows that there is an optimum weight for each muscle at which the work output is the maximum. When a muscle is stretched by a weight before it commences to contract (load), more mechanical work is possible than when the same weight is used as an 'after load'. In the case of 'load', (Fig. 3)

the work output rises with increase in the load, the limit being reached when the muscle is stretched to twice its normal resting length. Beyond this ceiling value, the muscle gives way suddenly and ruptures.

Fatigue: When an isolated muscle is excited through its nerve repeatedly, it becomes less and less excitable and finally becomes unresponsive (fatigued). The three phases of the twitch are lengthened as fatigue comes on and the relaxation period is very much prolonged, complete relaxation failing to occur. This leaves a contraction remainder which is the difference between the original resting length of the muscle and the length in the incompletely relaxed state. If the muscle is now excited by direct stimulation, it still responds showing that some block has developed at the neuromuscular junction. The nerve is practically indefatigable. The muscle cannot ordinarily be fatigued because complete exhaustion of the glycogen and 'fuel stores' does not occur since the fall in pH may block the complete utilisation of the fuel reserves. In the nerve muscle preparation, the neuromuscular junction is the weakest link and fatigue sets in at this site. This may be accounted for by a failure of the motor end plate region to repolarise. Fatigue after voluntary movements (in the intact body) is of synaptic origin (at the anterior horn cell). This is a built-in safety device (see synaptic transmission). Block at the neuromuscular region does not occur in this case.

Contracture: This term signifies a high and unalterable resistance of a muscle to stretch. This may arise out of structural abnormalities — fibrosis in a denervated muscle with loss of contractile elements, or fixation of joints. If it is due to a change in the muscle substance itself, it is called a myostatic contracture. In the abnormalities mentioned above, the defect is irreversible.

Physiological contracture is a reversible state brought about by thermal, electrical, mechanical and chemical factors. In this condition there is a localised depolarisation which is not propagated as in ordinary conduction of impulses. Much more has yet to be known about the underlying mechanisms. Denervated muscles also may show contracture as a result of hypersensitivity to circulating acetyl choline (Vulpian-Heidenhain phenomenon—seen in the tongue after sectioning the hypoglossal nerve).

Certain aspects of neuromuscular transmission are briefly touched upon while others are dealt with elsewhere. This synapse (Fig. 4) exhibits the chemical mode of transmission like any other mammalian synapse. Acetyl choline is liberated at the motor fibre terminals on excitation and it depolarises the motor end plate. Fatt and Katz demonstrated that even in the resting state, small packets of acetyl choline are released and the well known miniature end plate potentials are set up. A group of conditions have been clinically recognised and described under the term motor neurone disease. Here, only those that result from the involvement of the lower motor neurone are described, though upper motor neurone diseases are also to be included under this term.

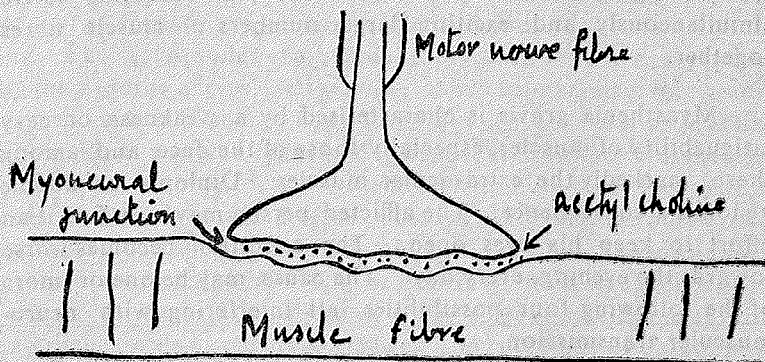


Fig. 4, Motor end plate

Progressive muscular atrophy and anterior poliomyelitis are two well known conditions affecting the anterior horn cells. The former is a progressive, degenerative and chronic disease which, if it involves the muscles of respiration, culminates in death. Poliomyelitis is an acute infective process resulting in quick destruction of the lower motor neurone. In the former condition,

certain abnormal muscular activity is seen. Fibrillation means the irregular and asynchronous twitchings of a few muscle fibres at a time when they are functionally denervated by the disease process and can be accounted for by the increased sensitivity of denervated structures to circulating acetyl choline. It can be detected only by recording the electrical activity in the muscle fibres by means of concentric needle electrodes placed in the belly of the muscle. It cannot be visually made out, Fasciculation which is mistakenly called fibrillation by clinicians, is a visible phenomenon and can be seen through the skin. The synchronous action in a squad of muscle fibres (of a motor unit) resulting from the irritation of the motor neurone, is held to be the underlying basis of this symptom. Synchronisation means the 'locking up' of a number of motor units, all becoming active simultaneously and exciting large numbers of muscle fibres together.

Myasthenia gravis is characterised by a weakness or easy fatiguability of muscles, especially those of the face and among these, markedly the extra-ocular muscles. Diplopia or double vision is a consequence. The afflicted person may even find it an effort to keep his eyes open. The condition becomes worse towards the evening, every day. The cause may be one or more of the following four possibilities, all interfering with neuromuscular transmission.

A curare-like substance may be present in the circulating blood and it may cause blocking of the action of acetyl choline by a competitive inhibition at the reactive sites on the motor end plate of the muscle. Curare-like drugs increase the severity of the symptoms, while anticholine-esterases ameliorate the symptoms. It is possible that the thymus which persists in these patients may elaborate a curare-like agent. Though thymic extracts do not contain any such substance, they aggravate the condition, but this is said to be due to the potassium in the extracts. Thymectomy has also been practised as a curative measure. Secondly, there may be a deficient production or release of acetyl choline and the small quantities released are conserved with the aid of anticholine—esterases like prostigmine which is used therapeutically. Thirdly, the motor end plate may

become refractory to the action of acetyl choline and lastly, there may be an excessive anti-choline esterase activity.

In myotonia, relaxation after contraction is incomplete. Unlike myasthenia, it improves towards the end of the day. The underlying basis is one of prolonged contraction arising out of a sustained activation of muscle fibre membrane.

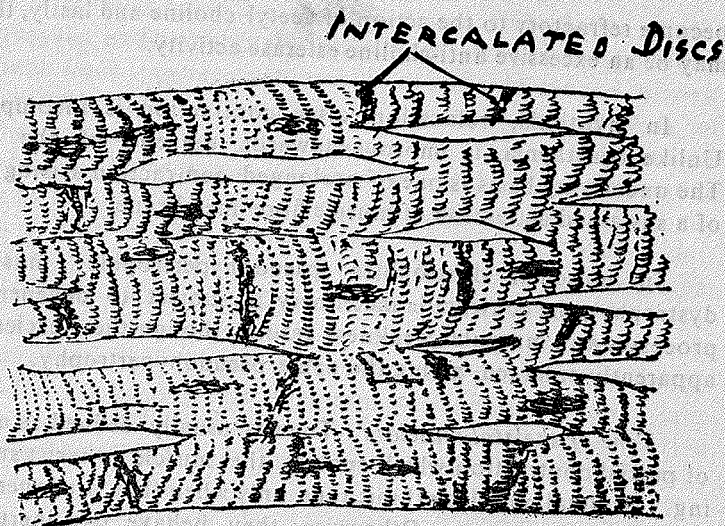
In muscular dystrophies (pseudohypertrophic muscular dystrophy), the contractile machinery is subject to degenerative processes and muscular weakness results though the muscles are apparently enlarged, giving the name pseudohypertrophy.

Tone of skeletal muscles: Tone is usually defined as a state of partial contraction which enables the muscle to resist stretching. Skeletal muscles exhibit tone only when they are innervated by their motor nerves. Otherwise, they behave like inert substances such as rubber. Tone is maintained by nervous mechanisms like the stretch reflex and is dependent on the presence of end organs in the muscle like the muscle spindle and the tendon organ. Tone is lost in diseases affecting the lower motor neurone and also when cortical area 4 is ablated or when the medullary pyramids are sectioned. On the contrary, it is exaggerated in lesions of area 6 of the cortex or when there is a lesion in the internal capsule as occurs in the well known clinical condition of hemiplegia. Cerebellar lesions also cause disturbances of tone. Decerebrate rigidity (experimentally induced) in animals affects the tone of the antigravity muscles. In Parkinsonism, there is a markedly increased tone of muscles which goes by the name rigidity or spasticity. Hypertonus is of two kinds — clasp knife type, as in hemiplegia and leaden pipe type in Parkinsonism.

Cardiac muscle was formerly considered to have an inherent tone, but this has been shown to be an erroneous impression. In reptilian heart, there is a sub-endocardial layer of plain muscle which probably is responsible for tone in such hearts.

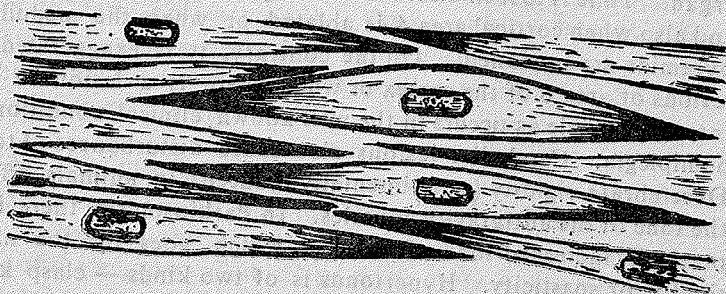
Red and White muscle fibres: In avian skeletal muscle, two types of muscle fibres have been recognised. The red (dark) variety has more myoglobin and high enzyme content especially

A



Cardiac Muscle

B



Plain Muscle Fibres

Fig. 5

of cytochrome oxidase. Fibres of this kind contract more slowly and fatigue less readily and also are tetanised at a lower frequency of stimulation than the white fibres (the pale type). Structurally, the former are more granular in appearance

with prominent longitudinal striations. The white fibres have more pronounced cross striations. In the human being, such differentiation does not seem to obtain. In animals with the two types of fibres in their muscles, the flexors which contract faster have a preponderance of white fibres, whereas the slower acting extensors are mainly composed of red fibres.

CARDIAC MUSCLE FIBRES

The heart muscle fibres (Fig. 5A) exhibit all the structural features of the skeletal fibres except for some differences. Unlike skeletal muscle fibres, these cells show branches which meet those of other cells. The cell boundaries are not easily made out. The heart muscle, though anatomically not a syncytium, can on functional grounds be considered to be so. Some aspects of the physiology of the cardiac muscle are discussed separately. (Vide Cardiovascular system).

PLAIN OR UNSTRIATED MUSCLE

The single plain muscle fibre (Fig. 5B) or cell is an elongated spindle-shaped cell with a widened or thicker central part and tapering ends. Longitudinal striations, owing to the presence of myofibrils, are seen in this type of muscle. Most important feature, however, is the absence of cross striations unlike in the other two types of muscle. The nucleus is cylindrical or rod-shaped with pointed or rounded ends and is situated slightly eccentrically in the cell. Many nucleoli are seen in it. When a contracted cell is fixed and examined, the nucleus may show folds. The size of a plain muscle cell varies from tissue to tissue — about 20μ as in the walls of blood vessels but it can be as long as 0.5 mm in the full term uterus, the width being about 0.2 mm at the thickest portion. Glycogen is found in the cell substance and can be revealed by special histochemical techniques — fixing in absolute alcohol and staining with Best's carmine method. In ordinary preparations, glycogen is dissolved out leaving blank spaces. These cells are surrounded by connective tissue. More often, bundles of plain muscle fibres are surrounded by elastic connective tissue. Fibroblasts may also be seen in between bundles. In ordinary haematoxylin—eosin stained sections, plain muscle fibres have a more meaty appearance than connective tissues.

To differentiate fibroblasts from plain muscle fibres, either Van Geisen's stain or Mallory's stain is used. The muscle fibre appears red and blue respectively, with the two stains.

The plain muscle fibre is, *in most cases* innervated by two sets of nerve fibres, one excitatory and the other inhibitory in action. These nerve fibres form plexuses in close association with the muscle tissue (for details see Autonomic Nervous System). In view of the close association of the nerve plexuses and the muscle fibres, it is not possible to say which properties of the plain muscle are due to themselves and which, due to the nerve fibres. There is no drug like curare to cause a block between nerve fibres and plain muscle fibres to enable the properties of these cells to be studied exclusively.

Plain muscle fibres are found in the walls of the alimentary canal and its sphincters, in the walls of the blood vessels, in the respiratory passages, arrectores pilorum muscles in the skin, around the pupil in the eye, and in the ciliary body of the eye,—to mention some of the organs and tissues.

Two physiological properties are very characteristic of plain muscle fibres — tone and rhythmic contractions. To this may be added conductivity from one fibre to the next, even without any apparent protoplasmic connections between the two.

Plain muscle, left to itself, even after denervation, exhibits a state of tonus or partial contraction and will resist to a varying extent, depending on the degree of tone, any attempts to stretch it. This tone is subject to the influence of drugs of the parasympathomimetic and the sympathomimetic groups. Which group increases the tone and which depresses it will depend on the organ in which plain muscle fibres reside. Maintenance of tone under isotonic conditions does not seem to require extra uptake of oxygen, but under isometric conditions, the greater the tone higher will be the oxygen requirement. Drugs which raise the tone, as well as forces causing stretch of plain muscle, will increase the oxygen consumption. The inherent tone of arteriolar blood vessels even when denervated, is a good example of this property.

When certain varieties of plain muscles are stretched, they exhibit regular or rhythmic contractions both in vitro and in vivo. The intestines exemplify this property. The rhythmicity is of muscle origin and not nervous. Ureter, gut and the gravid uterus show rhythmical activity.

The sluggish response to excitation of any kind distinguishes plain muscle from the other two kinds. High chronaxie is also a distinctive property. Summation of the effects of stimuli rapidly applied and longer refractory period, summation of subliminal stimuli (latent addition) are some of the features of plain muscle activity. Nerve stimulation liberates a chemical transmitter which, acting on the muscle tissue, brings about a response. Distension by the contents of hollow viscera (intestines, uterus and bladder) is a potent excitant.

Conduction from one muscle fibre to another is a remarkable feature. This seems to be made possible by protoplasmic bridge like processes between one cell and another.

Temperature changes have influences similar to those in the skeletal muscle. The chemical changes underlying muscular contraction, most probably are the same as in skeletal muscle, though the chemical constituents are present in lesser concentrations than in striated muscle.

It now remains to compare the three types of muscle as regards their structural and functional aspects. (*See page 96*)

5

	Striated, Striped, Voluntary or Skeletal muscle	Plain Unstriated tary or Visceral muscle	Cardiac muscle
1. Longitudinal Striations	present	present	present
2. Cross Striations	present	absent	present
3. Shape of fibres	cylindrical	spindle-shaped	Quadrilateral cells with branches.
4. Nucleus	elongated oval nucleus with rounded ends, situated peripherally in the fibre just under the sarcolemma.	one oval nucleus somewhat eccentrically placed in the cell.	one nucleus with flattened ends and centrally placed in the fibre.
5. Control	Under voluntary control mostly, though reflex control also occurs.	not under voluntary control.	not under voluntary control.
6. Nervous system in control.	Pyramidal tract. This type of muscle is nerve operated.	Autonomic nerves Nerve regulated.	Autonomic nerves Nerve regulated.
7. Effect of drugs.	Not much affected.	Very susceptible to drugs action.	Very susceptible to drug action.
8. All or none behaviour	Individual fibre contracts in 'all or none' fashion.	The single plain muscle cell may obey this law.	The whole heart muscle takes part in contraction in an 'all or none' manner

RESPIRATION

The term, respiration, includes all the processes by which tissues obtain oxygen from the atmosphere and liberate carbon-dioxide into the external atmosphere. These occur in two stages. In external respiration, the blood in the pulmonary capillaries exchanges its carbon-dioxide for the oxygen in the alveolar air of the lung, whose contents are replaced at every breath by the entry of atmospheric air, which displaces an equal volume of air, previously in the lungs. In internal respiration, the tissues abstract the oxygen from the blood in the capillaries and give off their carbon-dioxide load to the blood. The tissues having obtained oxygen from blood, make use of it through a number of metabolic steps, to derive energy for the various needs of the body.

PHYSIOLOGICAL ANATOMY OF THE RESPIRATORY TRACT

This extends from the external nares (nostrils) to the alveoli of the lungs. The nose is a chamber formed by cartilage and bone, and lined by squamous stratified epithelium in the vestibule of the nose. Some coarse hairs are also present at the entrance to the nose. These may assist in preventing large particles of any material from entering the nose. The rest of the nose has pseudo-stratified columnar ciliated epithelium, with serous glands underneath. Mucus-secreting goblet cells are also present. The shape of the nasal cavity is maintained by the bony and cartilaginous elements in its walls. The nasal cavity has the role of warming and moistening (humidifying) the inspired air, as it flows past the mucous membrane. The ciliary epithelium traps and conveys dust and other particles towards the oesophagus, to be disposed off by way of the alimentary tract. Ciliary movement is compared to that of the windswept field of grain stalks. It does not depend on nervous mechanisms but is susceptible to chemical influences. It is inhibited by a fall in temperature. Anaesthetics depress ciliary movement. Sedatives also have same action.

The pharynx is a common passage for the food bolus, as well as the respiratory air. Ciliated epithelium is present in the nasopharynx. The larynx is more or less a rigid structure, on account of its cartilages. Stratified epithelium lines the part above the vocal cords, but ciliated type is seen below. The vocal cords themselves are covered by stratified epithelium. The space between the two cords is known as glottis, which widens and narrows down during inspiration and expiration respectively, on

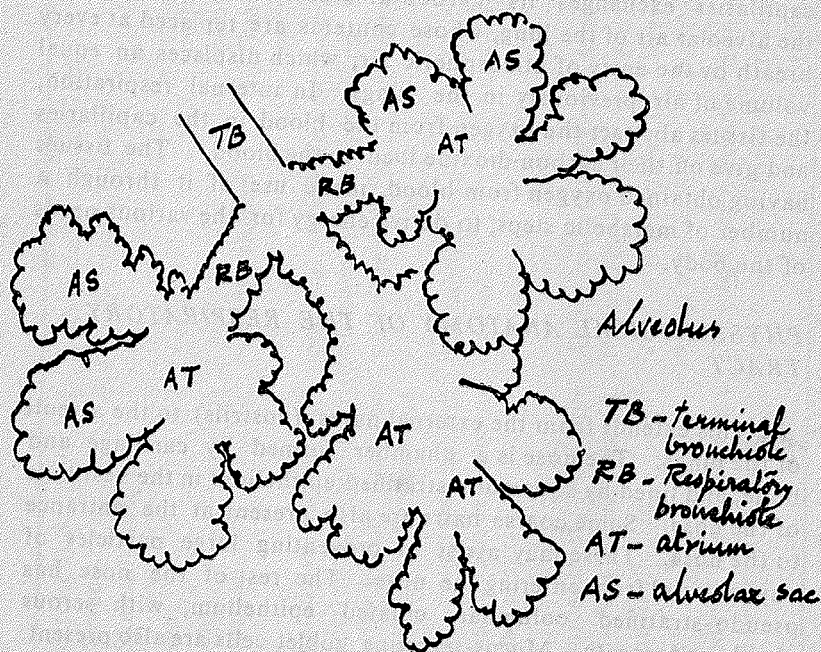


Fig. 6 Finer Subdivisions of the Lung

account of muscular action. The lower part of larynx is continuous with the trachea, which has cartilaginous rings in its wall, keeping it always open for the passage of air. Each ring has a gap in the posterior aspect. Ciliated epithelium is seen on the inner surface of the trachea. Goblet cells and serous glands lie under the epithelium. Elastic tissue is also present in the walls of trachea, as also in the still lower respiratory passages. The bronchi, one for each lung, exhibit the same histological features

as trachea, but there are no cartilaginous rings in the walls—only small pieces of cartilage are there, as if embedded, so as to maintain the patency of the passages. The glands and goblet cells diminish in number in the finer bronchioles of the bronchial tree. The terminal bronchioles lead into the respiratory bronchioles, which do not have a rigid structure (no cartilage at all) and also are lined by flattened or cuboidal and non-ciliated epithelium. The nonrespiratory portion of the respiratory passages which act as mere passages or conduits of air, ends at the junction between the terminal and the respiratory bronchioles — this is shown by the change in the type of epithelial lining. In the latter, flattened epithelium replaces columnar type. The respiratory bronchiole (Fig. 5) ends in a few alveolar ducts. Each duct (walls very thin and taking part in gaseous exchange) leads on to a chamber (atrium), each one of which opens out into a large number of diverticula — the alveolar sacs in whose walls are present the numerous alveoli. The divisions of the bronchial tree, are as follows :

Bronchi → small bronchi → terminal bronchioles (with sphincter action) → respiratory bronchioles → alveolar duct → atrium → alveolar sac → alveolus.

Some alveoli arise directly from the respiratory bronchioles as well as alveolar ducts. An alveolar sac is of diameter 0.075 to 0.125 mm. It has been estimated that there are about 750,000,000 alveoli in the two lungs, with an epithelial surface of 55 sq. metres available for respiratory exchanges.

The term, lung unit (primary lobule), refers to a respiratory bronchiole along with its branches and terminations.

Blood supply : The bronchial arteries arising directly from the thoracic aorta supply blood for all the larger passages in the lung upto the commencement of the respiratory bronchioles. The venous blood from these structures is drained by the azygos vein (right lung) and the left superior intercostal vein or accessory semi-azygos vein (left lung). Some blood from the bronchial arteries may drain into pulmonary veins in the border zone. The pulmonary artery, the lung capillaries and the pulmonary veins,

take care of the blood supply to the respiratory portions of the lungs. In the border areas (between terminal and respiratory bronchioles), anastomoses of blood vessels of bronchial and pulmonary systems, occur.

The nerve supply to the plain muscle of the lung passages is from vagus and the sympathetic fibres. The former, on excitation, brings about broncho-constriction as well as increased secretions of the glands. Sympathetic action causes broncho-dilatation, and sympathomimetic drugs are used to relieve bronchial spasm in asthma.

THE MECHANICS OF RESPIRATORY MOVEMENTS

The respiratory centre sends down volleys of impulses to the inspiratory muscles at intervals, to bring about inspiratory movements of the thoracic cage, alternating with expiratory excursions. The lungs which always fill the thoracic cavity, expand during inspiration and 'contract' during expiration, in a completely passive manner. In an adult, there are 16-18 double movements (inspiration followed by expiration) per minute. In the new born, the rate is much higher — 40 per minute.

Respiration is said to be of two types, depending on the prominence of the respiratory movements in the abdominal and thoracic parts of the body. In the male adult, respiration is said to be abdominal in type, since the movement of the diaphragm and the abdominal muscles are very prominent. This type is said to occur in males and young children. In women, the upper part of thorax is more active in the respiratory movements and they are said to have the thoracic type of breathing. During pregnancy, excursions of abdominal muscles are severely limited, permitting only thoracic movements. In inspiration, the thorax expands in all three directions—anteroposterior, lateral and vertical. In expiration, these changes are reversed.

The main muscles which, by their contraction, bring about inspiration are — the external intercostals and the diaphragm. Several other muscles (accessory) that contribute to the enlargement of the thorax are — the sternocleido-mastoids and the

scalene muscles of the neck mainly, and the pectoral muscles. It is said that in violent exercise, even limb muscles may take part in the respiratory movements. In contrast, expiration in restful respiration is a passive process, the elastic recoil of the thoracic cage bringing about the diminution of the size of the thorax without the intervention by muscles. However, in forced expiration, the internal intercostals come into action. The abdominal muscles, the external and internal oblique muscles and the rectus abdominis are, so to say, expiratory muscles, as they promote expiration when activated. The diaphragm is innervated by the two phrenic nerves, one on either side of the neck and arising from the 3rd, 4th and 5th cervical spinal cord segments. The intercostal muscles are innervated by the intercostal nerves arising lower down from the spinal cord. Any injury, such as transection of the spinal cord above the 3rd cervical segment, bring about paralysis of all the respiratory muscles. In polio-myelitis, when the spinal motor neurones giving off motor fibres to the respiratory muscles are involved in the disease process, artificial respiration, as in an 'iron lung', will have to be resorted to.

To repeat, inspiration is brought about by a concerted action of the inspiratory muscles. Keith has divided the thorax into four zones or regions for purposes of study of the movements in detail. They are:

- 1) The first pair of ribs and the manubrium—the operculum or lid of the thorax.
- 2) The upper costal series—from the 2nd pair to the 5th pair of ribs.
- 3) The lower costal series—from the 6th pair to the tenth pair of ribs. The diaphragm is included in this region.
- 4) The floating ribs and the abdominal muscles.

- 1) In the beginning of the inspiratory movement, the scalene muscles and the sterno mastoid muscles contract and lift the operculum, to occupy a more horizontal position and also to fix its position, so that the lower ribs will be elevated

towards it when the external intercostals contract. The movement of the operculum also brings about a slight increase in the antero-posterior diameter of the thorax at this level. In old age, because of ankylosis of the costosternal joints, movement is restricted.

- 2) The external intercostal muscles arise from the lower borders of the ribs above and run downwards and forwards to be inserted into the upper margins of the ribs below. Contraction as such of these muscles which bridge the gap between two ribs lying one above the other, brings the two nearer to each other. But, in view of the fact that the first pair of ribs is elevated, these muscles cause an elevation or lifting of the ribs. Each pair of ribs is lifted to lie nearer to the pair above it. Each pair of the ribs (2nd-5th) is longer, more oblique in direction and makes a sweep more outwards, than the pair above it. The action of the external intercostals not only elevates the ribs, but also makes them perform a so-called bucket-handle movement or rotation about an axis parallel to their necks, as well as another in an antero-posterior direction along a line joining the neck of the rib with the midpoint of the sternum at the level of the attachment of the rib to the sternum. The plane of the rib becomes more horizontal. This type of rib movement brings about an enlargement of the thorax, both in the antero-posterior diameter, as well as the transverse diameter.
- 3) In the case of the lower costal series, due to the action of the intercostal muscles, the ribs execute a rotation about an oblique axis passing through the midpoint of the sternum and the neck of the rib. The movement here again is of the bucket-handle type causing an increase in the lateral dimension of the thorax. In view of the oblique position in which the lower ribs converge on to the lower part of the sternum, the elevation of the ribs causes an actual shortening of the antero posterior diameter. The subcostal angle tends to become widened and this will draw the sternum backward.

The diaphragm is the chief muscle of respiration. Its contraction contributes to increase the lung volume, even in restful

inspiration, by about 60% of the tidal volume. During contraction, in quiet breathing, the dome of the diaphragm descends by about 1 cm. The shape or convexity of this muscle does not change during contraction, so that it can be considered to be a hemispherical or convex piston moving up and down inside the thorax. Consequently, a downward excursion of 1 cm. by the dome of the muscle, causes an increase in the thoracic volume (lung volume) by about 270 cubic cm., taking the cross section of the thorax at the level of the diaphragm to be about 270 sq. cm. In maximal inspiration, the muscle descends by as much as 3 cms. Thereby the increase in the lung volume is more than 800 cc. As the diaphragm descends, its peripheral parts contract and peel away, as it were, from the inner aspect of the ribs (level of 4th and 5th ribs), but preserving the shape of the whole muscle without flattening it. The costosternal part, as it comes down, pushes the abdominal viscera downwards and forwards, till the resistance offered by the abdominal wall (muscles) causes diversion of this force to push the sternum upwards and forwards. The lowering of spinal or crural part of the muscle, results in an increase in the vertical diameter. In the erect posture, the abdominal organs hinder its upward movement, as in expiration. In the recumbent posture, the viscera displace it upwards. In visceroptosis (dependent state of organs in the lowest position in abdomen), because of traction on the diaphragm, respiration is mainly of the thoracic type.

- 4) The floating pairs of ribs are embedded in the abdominal wall and they move outwards during inspiration, as the abdominal muscles relax.

Expiration in eupnic or restful breathing is a passive process. The relaxation of the muscles of inspiration, assisted by the weight of the ribs, restore the expiratory position of the thorax. In forced expiration, the internal intercostal muscles come into play, promoting active diminution in the size of the thorax. These muscles bring down the ribs from their raised positions.

Role of the Lungs in the respiratory movements: The two lungs play a passive role in respiratory movements. They expand to fill the thorax during inspiration and contract during expira-

tion. The lungs are enabled to completely occupy the thorax because of the negative intrapleural pressure, which keeps the parietal pleura always in contact with the visceral pleura which is inseparable from the lungs. As the thoracic wall moves outward during inspiration, the lungs follow to fill the newly created space. But the expansion of all the regions of the lung is not a direct consequence of thoracic enlargement. While the outlying parts of the lung expand directly as space is created next to them, in the case of 1) the dorsal surface of the apex of the lung, 2) posterior surface of the lung in contact with the vertebral column, 3) mediastinal surface of the lung, these regions expand because the other parts of the lung enlarge and move away to provide room for the former to occupy. In view of the immobility of the dorsal part of the apex caused by the lack of space to expand freely, it often becomes the focus of tuberculous infection. Also this part does not take part much in oxygenation of blood and its resistance to infection is diminished so that infection finds a nidus here.

Each lung consists of three zones which vary in the degree of expansibility during inspiration. a) A non expansile root or hilar zone, containing bronchi, pulmonary vessels and lymphatics. b) A region of maximum thickness or depth consisting of blood vessels, bronchial branches radiating outwards and lung alveoli varying in expansibility and more and more expansile towards the periphery. c) The outer or subpleural zone of about $1''-1\frac{1}{2}''$ of maximum expansibility.

As the lungs expand during inspiration, the root or hilus of the lung moves downwards, forwards and laterally. Each bronchus and its branches are stretched lengthwise and the smaller branches diverge away from each other. The passages also dilate with a peristaltic movement occurring in them. The apex of the lung moves downwards. The trachea also undergoes elongation. The vocal cords are abducted. The ala nasi may get pinched during inspiration and the soft palate is pushed towards the mouth. The passive manner in which lungs expand following the inspiratory enlargement of the thoracic cage, results in a negative intrapulmonary pressure in inspiration. Since there is a free communication between the lung passages and alveoli on

one hand and the atmospheric air on the other, air from outside rushes into the lungs. Movement of air occurs in the opposite direction during expiration. The lungs have no active role in bringing about the movement of air in either direction.

Respiratory movements affect almost all parts of the respiratory tract, though in some, the changes are very slight.

The pressure within the lungs (Intrapulmonary pressure) changes during the respiratory excursions of thoracic wall. In quiet respiration, it ranges between -2 mm Hg in inspiration to $+3$ or 4 mm Hg in expiration. In forced inspiration the pressure may fall to -30 mm Hg or -40 mm Hg and in maximum expiration it may rise to $+10$ mm Hg and even upto $+40$ mm Hg. In coughing, pressures as high as $+40$ mm Hg have been recorded. These pressures can be determined by inserting a metal or glass tube in one nostril, the other nostril and the mouth being closed and the nasal tube being connected to a mercury manometer (the sign before the value indicates that it is subatmospheric).

Intrapleural or intrathoracic pressure: The lung is covered by two membranes, the pleurae. The layer lining the inside of the thoracic cage is known as the parietal layer and the other covering the lung parenchyma and adherent to it is named the visceral pleura. A potential space, the intrapleural space, exists between the two pleural layers. A small quantity of serous fluid may occupy the space. The pressure in this situation is always subatmospheric, whether inspiration or expiration takes place. It is measured by inserting a sterile hollow needle between the two pleurae and connecting it to a manometer. A small volume of air is introduced between the pleural membranes, before readings of pressure are noted. The respiratory variations are as follows:

ordinary inspiration	-6 mm Hg.
ordinary expiration	-2.5 mm Hg.

It is to be noted that this pressure is always negative or subatmospheric. Even in maximal respiration it remains negative,

both during inspiration and expiration. The pressure is sub-atmospheric on account of the tendency of the lungs to recoil and move away from the parietal pleura.

Maximal Inspiration (glottis closed) —40 mm Hg.
Only in the following contingency (not normal) it can become positive

Maximal Expiration (glottis closed) +40 or +50 mm Hg.

The importance of the negative intrathoracic or intrapleural pressure lies in the fact that the lungs are always maintained in a stretched state so as to fully occupy the thoracic cage. Secondly, the subatmospheric pressure exerts an aspirating or suction effect, especially on the blood contained in the abdominal veins, so as to facilitate venous return to the heart. The intrapleural pressure is more negative in the diaphragmatic regions of the thorax where lungs can expand freely, than in other parts.

Changes in the lungs at birth: Before birth, the foetal lungs are airless and virtually solid organs. A little fluid may be contained in the functionless alveoli. The thorax itself is unexpanded. Very little of blood flows through pulmonary vessels. The ductus arteriosus provides a shunt by which blood is enabled to by pass the pulmonary vessels. Respiratory movements have however been observed in the foetal lung. Injections of India ink or thorotrast into the uterine cavity result in these materials being drawn into the lung passages as a consequence of thoracic movements.

At birth, respiratory movements become more forcible, the diaphragm descends and the external intercostal muscles contract. The thoracic cavity is enlarged and the intrapleural pressure falls steeply necessitating the expansion of the lungs, since the two pleurae are virtually inseparable. Only after the first few days after birth, full expansion of the chest is attained. After this, the lungs are always pressing on the inner aspect of the chest wall in spite of their inherent tendency to recoil to a smaller size, because of the negative intrapleural pressure which has been established when active respiratory movements of the thorax were initiated.

Expulsion of foreign material which may find its way into the respiratory tract is effected by three mechanisms.

- a) cough reflex — Irritant gases or particles which enter the trachea stimulate the sensory nerve endings in the mucosa and set up the cough reflex. The most sensitive spots for eliciting the cough reflex are the mucosa of the region of the bifurcation of the trachea and laryngeal mucosa. Vagal afferents in the lungs, nerve endings and even the auricular branch of the vagus in the pleura may also be stimulated, resulting in the cough reflex.

The reflex consists of a short inspiration followed by closure of the glottis and forcible expiratory effort following the closure. A high pressure is built up in the lungs. The glottis opens suddenly and the offending material is thrown out through the pharynx and nose or even through the mouth. If the expulsion is not completed, the act of coughing is repeated. Sneezing is a closely related phenomenon, except that it involves only the nose and nasopharynx and it also is directed towards the removal of irritating material. In this case the glottis is however open, the entry of air into the mouth during the expulsion stage is blocked by the lifting of the tongue to lie against the soft palate. Later, the mouth is kept open and some air may escape out through the mouth. The stimulation of the trigeminal nerve endings in the nose brings about this reflex. Yawning, while it may arise from fatigue or boredom, may also have a psychic basis — seeing another person yawn may be 'contagious'. It consists of a deep inspiration with the mouth kept open followed by sighing caused by a long drawn out expiration.

- b) The bronchioles exhibit a peristaltic movement to slowly shift irritating material. The ciliary movement is a complementary mechanism.
- c) The lung tissue shows a large number of macrophages (large amoeboid cells), which phagocytose small particles (Neutrophils deal with bacteria inhaled in the air).

Hiccough or hiccup is a spasmodic and purposeless contraction of the diaphragm, occurring as a reflex effect. Afferent

nerve endings are present in the diaphragm and the phrenic nerve is the efferent limb. Sub-diaphragmatic abscess and basal pleurisy are conditions in which intractable hiccough is a symptom. Even in normal people it may occur without an obvious cause. Drinking liquids very rapidly may bring it about. Inhalation of air containing 7% carbondioxide abolishes this, most often.

Collateral respiration: It is very likely that cross communications (pulmonary vents) may exist between neighbouring alveoli. When a small passage like the alveolar duct is obstructed, the alveolar sac belonging to it may get filled by air entering it from other sacs, resulting in collateral respiration.

LUNG VOLUMES AND CAPACITIES

It is often necessary to assess the physical capacity of a human subject, for work as well as endurance in adverse environment. For selection of candidates for the armed forces, police service and other vocations, certain tests have been evolved in order to judge the fitness of the applicants. Standards for normal values have also been established to enable the separation of the fit from the unfit. The following account deals with the various criteria involved in what have come to be known as 'Lung function tests'.

1. Tidal air or volume — This is the volume of air that is either breathed in or out, in eupnoea or quiet breathing. In an adult, it has an average value of 500 cc. This of course increases upto a maximum of eight times the resting value, in muscular exercise. It is diminished in diseases affecting the cardiovascular and respiratory systems. Athletes have a larger tidal volume in comparison with sedentary people.
2. Inspiratory reserve capacity — This is the amount of air that is breathed in with maximum effort after a normal expiration. It is about 3000 cc. If the normal (inspiratory) tidal volume is deducted from the value of the inspiratory reserve capacity, the remainder is known as the inspiratory reserve volume which was formerly termed complementary air.

3. **Expiratory reserve volume** — This refers to the quantity of air breathed out with utmost effort after expelling the normal tidal volume. The average normal value is around 1000 cc.
4. **Residual volume or residual air** — The volume of air which remains in the lungs even after the maximum expiratory effort, is the residual volume which amounts to 1000–1500 cc. Functional residual capacity is the volume of air which remains in the lung after a normal expiration—2500cc.
5. **Vital capacity** is the quantity of air that is collected when the subject breathes out most forcibly after the deepest possible inspiratory effort. It ranges between 3 and 5 litres, the actual value depending on certain factors like training for physical work, height, weight, body surface area, age and sex of the individual. Athletes have higher values. Women usually have lower vital capacities. It comes down with increase in age. Vital capacity expressed in terms of unit body surface area is a useful index. It is lowered in cardiovascular and pulmonary diseases. It is a much better or more dependable index of physical capacity than the time-honoured chest measurements and chest expansion in inspiration, which are very likely to be fallacious. An increase in the circumference of the chest may be achieved in a muscular subject, at the expense of an increase in the lung volume. The diaphragm may be drawn up with a contraction of the abdominal muscles. Vital capacity can also be derived as the total of inspiratory reserve capacity and expiratory reserve volume. The total lung capacity exceeds the vital capacity by the residual volume and is about 5–6 litres in adults.

Tidal air, expiratory reserve volume and vital capacity can be determined, using a simple Hutchison's water spirometer, or a Douglas' bag along with a gas meter. The Douglas' bag of 100 litres capacity is a rubber bag covered by cloth to make it nonexpansible. Inspiratory reserve capacity as well as the volume can be derived indirectly. The respiratory movements of the thorax or of the abdominal wall can be recorded on a smoked drum by means of a pneumograph (stethograph) which is made to encircle the thorax or the abdomen and is

connected to a Marey's tambour. The number of movements per minute can be read off from the graphic record.

Residual Volume or volume of lung at any moment: The subject breathes from and into a spirometer containing a mixture of oxygen and hydrogen in a known proportion and quantity, the exhaled carbondioxide being absorbed by sodium hydroxide. After a short while, a sample of the mixture in the spirometer is analysed and from the following quantitative relationship, the volume of nitrogen in the lung is obtained.

$$\frac{N_2 \text{ in sample}}{H_2 \text{ in sample}} = \frac{\text{Total volume of } N_2}{\text{Total volume of } H_2 \text{ (known)}}$$

Since N_2 forms 79% of the lung air, the lung volume can be calculated from the volume of N_2 in the lungs.

Alveolar air: This is the air enclosed in the lung alveoli which comes into equilibrium with blood in the lungs and is partially changed, as regards its composition, at every inspiration and expiration. Since every time inspiratory air is drawn into the lungs it adds some oxygen to the alveolar air and every puff of expired air removes part of the carbondioxide in the alveoli, the composition of alveolar air is different from that of either the inspired (atmospheric) or the expired air

	Oxygen	Carbondioxide
Alveolar air	14.0	6.0 (40 mm Hg tension)
expired air	16.0	4.0
inspired air	21.0	traces

(Figures are volumes per cent approximately.)

A sample of alveolar air is collected by blowing by mouth after a normal expiration, a further amount of air, forcibly down a Haldane's tube of 1 metre length and more than 2 cms inner diameter. The last portion of the expired air is quickly drawn into a previously evacuated sampling tube (alveolar air tube) of

Even in deep breathing with increased volume, calculation on the same lines as above will yield the physiological dead space air, whose variation reflects the extent to which fresh air is drawn into the lungs during inspiration. Anatomical dead space can be determined by preparing a plaster of paris cast of the respiratory passages in a dead subject and measuring its volume.

Pulmonary Ventilation : Alveolar ventilation per minute is given by the product of frequency of respiration and (tidal volume — dead space). The respiratory minute volume is given by multiplying the tidal volume and the respiratory rate. Actually, the tidal volume is derived from the respiratory minute volume. Expired air is collected over a known duration of time, in a Douglas' bag while the respiratory movements are being recorded. The volume of air collected per minute gives the respiratory minute volume and knowing the rate, the tidal volume can be calculated.

LUNG FUNCTION TESTS

As already mentioned in the introduction to this section, certain tests are used to weed out the physically 'below par' subjects from those deemed fit, for certain professions.

1. The rate of breathing, the depth of breathing (tidal air), the respiratory minute volume and the alveolar ventilation are determined.
2. Lung volumes and capacities have also to be determined.
3. An idea of the distribution of inspired air is obtained — how evenly the inspired air occupies the alveoli. This is assessed by the following procedure. The subject inspires pure oxygen once and expires slowly and steadily. The expired air is analysed for its nitrogen content. In the beginning, only pure oxygen (which was in the dead space after inspiration) was expelled. Following this, during a longer interval, the nitrogen concentration rose up and in the final and longest phase, nitrogen content remained steady or within limits. In the case of a non-uniform distribution among the alveoli, the nitrogen content rose up by as much as 12% in the third phase.

Ventilation perfusion ratio — Normally the alveoli in both lungs receive 4 litres of fresh atmospheric air in a minute. The blood flow through the capillaries of the lung is about 5 litres per minute (cardiac output). The ventilation perfusion ratio is therefore $4/5$ or 0.8. Whether or not this proportion actually exists in all the alveoli of the two lungs is what matters with regard to oxygenation of blood.

4. **Diffusing capacity of the lungs** — This is defined as the quantity of a gas (oxygen) which is transferred from alveolar air to the blood in the pulmonary capillaries, for every millimetre difference in tension between pulmonary venous blood and alveolar air. On account of non-uniformity of oxygen tension in the pulmonary capillaries and also the fact that no 'sample' of alveolar air can be representative of all alveolar air, the diffusing capacity as regards only of carbon monoxide is determined, the gas being chosen in view of the high affinity of haemoglobin for it. The diffusion of a gas depends on structural factors and also its physical characteristics, like solubility in water, temperature etc. Normal value in a young adult for oxygen ranges from 20 to 30 ml/min/mmHg.
- 5.a) **Maximum Breathing capacity**—This is the greatest volume of air that can be breathed per minute — by voluntarily respiring as deeply and as fast as one can, in a closed circuit, for about $\frac{1}{4}$ min. The value is between 80 and 170 litres per minute in male adults. It is less in females and it decreases with age.
- b) **Timed Vital Capacity**—It has been felt that a simple determination of vital capacity may yield an erroneous value, since the time factor is not controlled. The fractions of the total vital capacity that are expelled in the 1st, 2nd and the 3rd seconds expressed as percentages, are determined. Normal subjects expire 83% in the first second, 94% by the end of the next second and 97% by the end of the third second.
- c) **Maximum inspiratory and expiratory flow rates**: These rates have been found to be about 400 litres/min and 500 litres per min. respectively. There are other tests also described. It is not necessary always to do all the tests in every subject.

A word of caution is necessary as regards the utility and the limitations of these tests, which do not replace other procedures but only provide additional useful information. They only show if the lungs are able to discharge their function adequately but do not suggest or indicate what anatomical or pathological abnormalities are responsible for the deranged pulmonary function.

ARTIFICIAL RESPIRATION

In certain contingencies like drowning or during anaesthesia for surgery or after electrocution by a high voltage electric current, when respiration has ceased, it will be necessary to resuscitate or revive the affected person by instituting artificial respiration which is directed to stimulate and re-establish natural and spontaneous breathing movements. This should be done as soon as possible and no time should be lost. It will not serve any useful purpose if the patient had stopped breathing for longer than 6-8 minutes, since the viability (ability to keep alive) of the brain cells would have been irrevocably lost as they have been deprived of their oxygen supply. Though there are several methods for rendering artificial respiration, the common purpose is to aerate the lung and also to stimulate the quiescent or depressed respiratory centre. Also, the promotion of adequate circulation is aimed at. The older methods are — a) Schaffer's method — with the subject in the prone position, pressure is applied over the small of the back to promote expiration.

- b) Sylvestre's method — the patient is in the supine position during the procedure.
- c) Eve's rocking method — The subject is laid in a prone position on a rigid board and rocked about a pivot in the middle so that there is a see-saw movement.
- d) Holger Nielsen's technique — The patient is laid in the prone posture with his head turned to one side and resting on one hand which itself rests on the other hand, the elbows being flexed and the arms held overhead. The operator raises the subject's arms and then drops them. He then applies compression on

the chest below the shoulder blades. These two acts are carried on, one alternating with the other for about 12 times in a minute. The tidal volume is greater in this case than in Shaffer's method. Venous return is enhanced and so cardiac output is increased.

- e) Mouth to mouth method—The operator blows air into the lungs of the subject by placing his own mouth on the other's mouth. He then lifts his head to enable air to escape from the subject's lungs. He repeats the blowing of air twelve times per minute.

Mechanical means like the iron lung in which the whole body of the patient is enclosed in a chamber with only the head outside and the neck being surrounded by an air tight collar at the end of the chamber. The pressure inside the chamber is raised and lowered alternately (12 times per minute) by blowing in air from a pump and decompressing it. When artificial respiration has to be carried on for a long time, over several hours or even days, this is a very convenient and labour saving method.

A method of recent origin is to deliver electrical pulses at regular intervals to the phrenic nerve to effect the contraction of the diaphragm. This is a physiological method of artificial respiration since it simulates the natural mode of excitation of the diaphragm. Provided the stimulating electrode is accurately placed over the neck, to deliver electrical stimuli to the nerve, artificial respiration can be maintained for prolonged periods.

In natural respiration, it is the inspiratory phase which is active. In artificial respiration, expiration is actively promoted, inspiration being, so to say, passive. In view of this, the circulatory effects of active inspiration are absent. Venous return may actually be reduced during inspiration. With phrenic nerve stimulation, inspiration becomes an active phase. The use of the iron lung produces disparities in alveolar ventilation; not all of the alveoli are aerated to the same extent. Anoxaemia may result.

Damage to lungs may occur when artificial respiration is instituted with too great an enthusiasm and vigour. Lung alveoli may get unduly stretched and ruptured. Stretch receptors in the lungs (those concerned with the Hering-Brewer reflex) may prevent this to some extent. Air, which enters during over-distension of the lungs, may dissect through vascular spaces and leak out as air emboli. This is a possibility to guard against.

Artificial respiration should result in adequate ventilation of the lungs and also promote circulation, though this is not always possible since a method which helps the circulation may hinder the ventilation.

The use of 5% of Carbon dioxide in the mixture breathed during artificial respiration, helps in stimulating the respiratory centre, but this is contra-indicated and inadvisable when the respiratory centre is already depressed.

Artificial respiration is carried on in experimental animals which have been anaesthetised, by means of a respiratory pump which inflates the lungs to any desired extent (tidal volume can be varied).

PHYSICAL BASIS OF GASEOUS EXCHANGE IN THE LUNGS AND TISSUES

The transfer of gases between the alveolar air and the pulmonary capillary blood on the one hand and the capillaries and the tissue cells on the other, is governed entirely by physical principles, as enunciated by Boyle, Charles and others whose laws concerning the relationship between volume, pressure and temperature are too well known to need restatement in this context. It was held by Barcroft that the lung epithelium can secrete oxygen into the blood in the pulmonary capillaries, in conditions of hypoxia. The purpose of this section is to dispel such a notion. No expenditure of energy is required for gaseous diffusion from one compartment to the other. The tension gradient as regards a gas, between the two sides of either the lung epithelium or the capillary endothelium, is the main factor involved. In addition, the solubility of a gas in water, which is indicated by the absorp-

tion coefficient of gas and also the molecular weight of the gas, determine the diffusion rate. Thus, carbon dioxide diffuses thirty times as fast as oxygen, which is not very soluble in water. The diffusion coefficient of a gas has been defined as the volume diffusing per minute, per millimetre tension gradient. Thus,

	Diffusion coefficient of oxygen	Diffusion Coeff. of carbondioxide
At rest	23-45 cc	500 cc
During exercise	37-56 cc	800 cc

	PARTIAL PRESSURES (mmHg.)		
	Arterial blood	Venous blood	Alveolar air
oxygen	100	40	>100 (higher than 100)
carbon dioxide	40	46	40
Nitrogen	570	570	570
water vapour	47	47	47

Nitrogen is an inert gas as far as respiratory exchanges are concerned, though it is present to a greater extent than any other gas in the lungs. It is to be noted that the carbon dioxide tensions in arterial blood and alveolar air are the same. Though circulation through lungs may be quickened, as in exercise, the oxygen absorption and carbondioxide delivery do not suffer, as the diffusion rates also increase.

The following table gives the composition and tension of each respiratory gas in inspired, expired and alveolar airs, as well as in arterial and venous blood.

Composition (percentage approx.)

	Inspired air (atmospheric air)	Expired air	Alveolar air
oxygen	21.00	16.00	14.00
carbondioxide	0.04	4.00	6.00
nitrogen and other gases (See page 118)	79.00	*80.00	80.00

Partial pressures (tension in mm. Hg)

oxygen	160	116	101
carbon dioxide	—	28	40
Aqueous vapour	5	47	47
nitrogen	595	569	572
	760	760	760

*The increase of nitrogen content in expired air is due to greater absorption of oxygen than the output of carbon dioxide in the lungs (R.Q. < 1).

Absorption Coefficient is the volume in cc of gas absorbed by 1 cc of fluid at 760 mm Hg.

	Plasma	Whole blood
oxygen	0.023	0.0184
carbon dioxide	0.51	0.48

N. B. Only a very small quantity of oxygen is held in plasma in solution and this little is very important functionally.

$$\begin{aligned} \text{Diffusion rate} &\propto \text{absorption coefficient} \\ &\propto 1/\text{molecular weight} \end{aligned}$$

Content of oxygen and carbon dioxide (in cc) in 100 cc of arterial or venous blood :—

	Venous blood		Arterial blood	
	Total	in solution	Total	in solution
oxygen	12-14	0.1	19.0	0.24
carbon dioxide	52	3.0	48.0	2.5

TRANSPORT OF OXYGEN

Blood has one important function among its several roles, which is the transport of oxygen from the lungs to the tissues. It contains haemoglobin, the conjugated protein, having the unique property of combining with oxygen readily and also parting with its oxygen with equal ease. This is what makes haemoglobin an ideal respiratory pigment. Each molecule of

haemoglobin can take up two atoms of oxygen when the pigment is exposed to a high tension of oxygen. Thus 1 gm. of haemoglobin gets saturated with oxygen when it takes up 1.34 cc of the gas. Since the usual quantity of haemoglobin in blood is about 15 gms. %, 100 ml. of blood will combine with 20 cc of oxygen in the lungs. The actual saturation attained by haemoglobin is about 95%, since all the alveoli of the lungs are not aerated to the same extent. The tensions in venous and arterial blood and alveolar air have been presented previously and are given below.

	Venous blood in pulmonary capillaries (mm Hg)	Alveolar air mm Hg	Arterial blood mm Hg
oxygen	40 ←—	100	100

The arrow indicates the direction in which oxygen diffuses under the tension gradient of 60 mm Hg (100—40). The capillary blood shows a rise in oxygen tension with the diffusion of oxygen from the alveolar air and attains a value of 100 mmHg (95% saturation). In the tissue capillaries, the undermentioned tensions exist.

Tissue Capillary blood	Cells
100 mm —→	40—

Oxygen moves from blood to tissue cells. The oxygen saturation falls from 95% to 70%. The coefficient of oxygen utilisation is the fraction of the total content of oxygen in blood which is delivered to the tissues. Its value is upto 0.36, at rest.

The behaviour of haemoglobin and whole blood as carriers of oxygen from the lungs to the tissues can be advantageously studied by means of a dissociation curve, which is obtained as follows: A series of ten (or twenty) tonometers are taken and in each, one or two ml of blood is put and spread as a thin film on the inner surface of the tonometer. Each tube is exposed to a different tension of oxygen, from 10 mm to 100 mmHg. The quantity of oxygen absorbed by each sample (at the particular tension to which it is exposed) is determined and therefrom the

percentage saturation is calculated. A graph is plotted, representing tensions along the X-axis and the percentage saturation along the Y-axis. Similarly, a dissociation curve is obtained for an aqueous solution of haemoglobin.

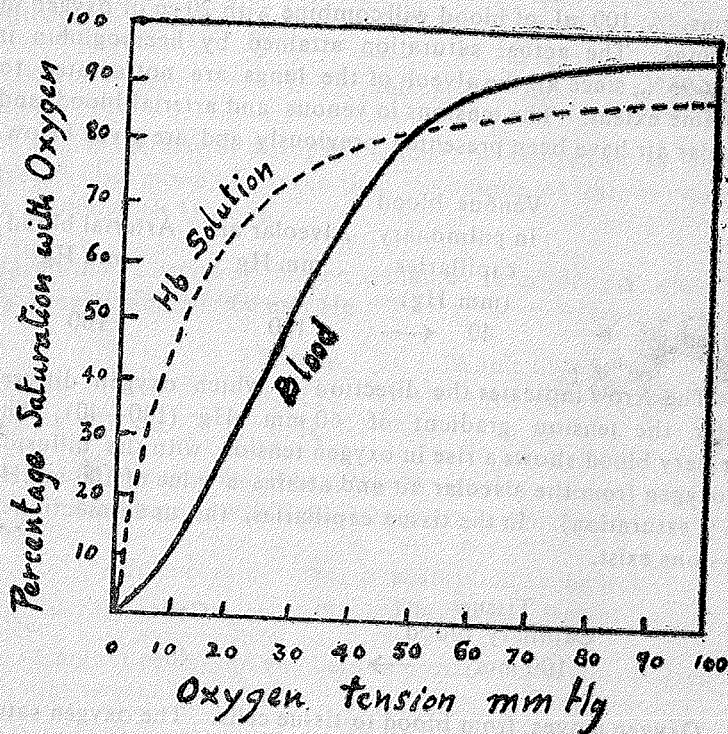
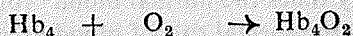


Fig. 7 Oxygen Dissociation Curves

The curve for whole blood: The usual range of tensions over which blood functions as a carrier of oxygen, while at rest, is between 100 mmHg (arterial blood) and 40 mmHg (tissue tension).

1. At 100mm tension, blood is only saturated to 95%. Further rise in tension does not appreciably raise the degree of saturation.

2. Relatively, not much reduction in the saturation occurs till tension falls to half the maximum value. At 70 mms, the saturation is 90%.
3. There is nearly a maximal absorption above 80 mm tension. Below 70 mm and above 40 mm tension, the curve shows a steep course. This is the functionally important part of the graph. It is in this range that blood parts with its oxygen freely, if necessity arises, as in muscular exercise. At lower tensions, not much more liberation or delivery of oxygen occurs.
4. The shape of the curve is S-shaped. This is due to the fact that haemoglobin exists in the blood stream as its polymer $(Hb)_4$. The uptake of oxygen occurs in conformity with four simultaneous changes, viz :



The progress of oxygenation in four concurrent steps, determines the shape of the dissociation curve.

The oxygen dissociation curve of foetal blood lies to the left of that for adult blood. Foetal haemoglobin has greater affinity for oxygen and yields the gas only at very low tensions.

In the case of the haemoglobin solution, the curve is of the shape of a rectangular hyperbola. The obvious inability of such a solution to act as an oxygen carrier is indicated by the occurrence of a fall in oxygen saturation of the solution, only when it is exposed to tensions much lower than what may ordinarily occur in the body. Haemoglobin enclosed in the red cell seems to acquire special advantages over haemoglobin freely dissolved in water. The curve for distilled water is a straight line showing that more gas dissolves at higher pressures of the gas, without a limiting value.

Not all the oxygen held by blood is in the form of oxyhaemoglobin. A very small quantity (0.3 cc per 100 cc blood) is dissolved in the plasma. First, under the tension gradient oxygen in the lung alveoli enters the plasma to dissolve in it and next, equilibrium is established between the plasma and the red cell. As more and more oxygen dissolves in plasma, more and more will leave the plasma to enter the cell to combine with the haemoglobin. Likewise, in the tissues, at first plasma gives off its oxygen to the tissues because of the difference in tensions between plasma and tissues. Oxyhaemoglobin dissociates and oxygen enters the plasma to dissolve in it to 'equalise' the tensions of oxygen between red cell and plasma. This goes on till oxyhaemoglobin parts with its usual or required volume of oxygen to the tissues. If blood were replaced by plasma or water as the circulating fluid, transferring the oxygen from the lungs to the tissues in sufficient quantities will require about 120 litres of fluid. This is many times the normal blood volume of 6 litres. This fact illustrates the special role of blood as an oxygen carrier.

The shape and position of the dissociation curve for whole blood is affected by the following factors. :

1. A change in pH, such as a lowering of it, will displace the curve to the right, causing it to be flattened. This implies that blood has a diminished affinity for oxygen. Accumulation of carbonic acid or lactic acid, as in exercise, brings about a shift to the right. This means that blood parts with more of its oxygen at the same tissue tension of oxygen.
2. A rise in temperature of blood will also cause a shift to the right and this particular effect is known as the Bohr effect.
3. A rise in pH of blood or a fall in temperature leads to a shift to the left. This implies that blood will not part with its oxygen as easily as in ordinary conditions and it will deliver less oxygen under the same tension gradient.
4. Inorganic salts in solution in plasma do not have any influence at all.

The demand for increased amount of oxygen by tissues is met as follows:—

1. Increased circulation rate — greater cardiac output.
2. Increase in coefficient of oxygen utilisation (at rest – 0.36) brought about by —
 - a) A shift to the right, of the dissociation curve, caused by the acids like carbonic acid, lactic acid etc.
 - b) Lowering of oxygen tension in tissues because of enhanced activity.
 - c) Opening up of more capillaries,

The coefficient of oxygen utilisation may be raised upto 50 times the resting value, in an athlete.

Cyanosis: This is a bluish discolouration of skin and mucous membranes, caused by the presence of large amounts of reduced haemoglobin (or other dark coloured derivatives) in the cutaneous or mucosal vessels. Cyanosis cannot occur when the total haemoglobin content of blood is less than 5 gms per cent. This is so because, at least 5 gms of reduced haemoglobin must be present in every 100 ml of blood for cyanosis to be manifest. Cyanosis is seen in anoxic and stagnant types of hypoxia. Two factors determine the degree of cyanosis —

- a) State of patency of cutaneous vessels. If these are constricted, cyanosis cannot be seen.
 - b) The pigmentation and thickness of skin.
- Cyanosis occurs in several pathological conditions.

HYPOXIA

Insufficiency of oxygen to meet the metabolic needs of cells has been termed hypoxia (formerly known as anoxia). This relative or absolute lack of oxygen may arise out of a number of circumstances which are grouped into four categories—

- | | |
|---------------------|------------------------|
| 1) hypoxic hypoxia | 2) anaemic hypoxia |
| 3) stagnant hypoxia | 4) histotoxic hypoxia. |

The last category is really not a state of hypoxia conforming to the foregoing definition of hypoxia. More about it shall be mentioned later. Hypoxia should be distinguished from asphyxia in that, in the latter there is, in addition, an excess of carbon dioxide in the blood. Hypercapnia is the term referring to accumulation of carbon dioxide per se in blood.

Hypoxic hypoxia: This term implies inadequacy of oxygen supplied for aerating pulmonary venous blood, arising from various conditions. Tissues are therefore made to 'suffer' on account of diminished oxygen availability for their needs.

- a) The inspired air contains less amount of oxygen than what occurs at places at sea level. As one ascends high mountains or in an aeroplane, the atmosphere one breathes from contains oxygen at lower and lower partial pressures with increase in altitude. The effects of low tensions of oxygen are felt at heights above 10,000 ft. above the sea level.
- b) The oxygen content of the atmosphere may be relatively lowered when it is vitiated by foreign gases as emitted by industrial establishments like factories, workshops etc.
- c) Diseases of the lungs may interfere with pulmonary ventilation which becomes inadequate leading on to hypoxic hypoxia. Anaesthetic and depressant drugs bring about changes in the rate and depth of respiration with consequent imperfect aeration of the lungs.
- d) Arteriovenous shunts like patent ductus arteriosus, patent foramen ovale or interventricular foramina cause bypassing of some amount of blood away from the lungs so that it fails to get oxygenated at all. When this blood mixes with what has passed through the lung capillaries, the degree of oxygen saturation of the latter is reduced. Thus, tissues receive blood not fully oxygenated.

Anaemic hypoxia: While there is no interference with the process of oxygenation of blood in the lung as may arise from

anyone of the causes of hypoxic hypoxia, the load of oxygen which the blood can carry away from lungs is diminished on account of one of the following causes:—

- a) anaemia of any cause with fall in haemoglobin content of blood.
- b) acute haemorrhage reduces the oxygen combining power, since the total haemoglobin content of the body has become less.
- c) In carbon monoxide poisoning or in nitrite and chlorate poisoning, part of the haemoglobin undergoes change to an inactive form as far as the oxygen combining function is concerned. So, the amount of the effective haemoglobin is reduced. The affinity of haemoglobin for carbon monoxide is stated to be 300 times that for oxygen. It is considered that anaemia as such is, physiologically speaking, a more tolerable condition than carbon monoxide poisoning of a limited degree, since in the latter, enzymes of the cytochrome system are affected by carbon monoxide. More than this, carbon monoxide hinders the remaining unaffected oxy-haemoglobin from giving up its oxygen. The dissociation curve is shifted to the left. Also, the chemoreceptor mechanism does not function, since there is no fall in oxygen tension.

Stagnant hypoxia: Sluggish circulation, as may happen in the undermentioned cases, may result in the capillary blood parting with most of the oxygen held by it — the coefficient of oxygen utilisation may be high in the beginning. But, when the severely de-oxygenated blood does not leave the vicinity of the tissues fast enough to permit flow of fresh amounts of oxygenated blood to deliver oxygen to them, stagnant hypoxia occurs.

- a) Congestive heart failure — generalised venous stasis.
- b) Local venous stasis due to a local mechanical obstruction.
- c) Surgical shock, wherein the blood pools in the peripheral vessels due to acute vasodilatation.

Histotoxic hypoxia: As already suggested, this is really not a hypoxic state, since oxygenated blood courses freely through all the vessels and hence oxygen can be taken up by tissues if only they could. The most important action of cyanides and barbiturates is to interfere with the action of oxidative enzymes of the cytochrome system — (cytochrome oxidase specially by cyanides and dehydrogenases in the case of barbiturates, morphine and anaesthetics). Hence, the oxidative processes in cells are either slowed down or blocked altogether. The oxygen abstracted from blood cannot be utilised and hence the tissue tension of oxygen does not fall and so blood flowing through the capillaries cannot part with its oxygen. It is evident that this state cannot really be considered as hypoxia. Mild histotoxic hypoxia may feature in fever states.

The foregoing four states of hypoxia can be studied by means of the oxygen dissociation curve of haemoglobin, to know the tensions of oxygen involved in gaseous transfer. The following table indicates in a qualitative way, the tensions of oxygen in arterial blood and in tissues in the four types.

The data in the tabular statement (p. 127) give an idea of the tensions of oxygen in arterial and venous blood, as well as in tissue fluid and the volumes of oxygen transferred to the tissues in the four types of hypoxia. The numerical figures are only indicative of the possible values as can be taken from oxygen dissociation curves for haemoglobin and also the range of values in the different types of hypoxia. It is not meant that the data should be considered as some kind of stand ard for memorising.

Mountain sickness: This is, properly speaking, high altitude sickness, brought on when one climbs high mountains or ascends in an aeroplane. The symptoms appear in untrained or unacclimatised persons, who rapidly reach levels above 10,000 ft. Slow ascent, allowing for adaptive changes to heights above 10,000 ft. may not bring about any marked symptoms. Permanent residents at very high altitudes of even more than 15,000 ft. as in the Andes mountains region of South America or the Alpine regions of Central Europe, do not suffer from the ill effects of high altitudes.

	Arterial Blood			Venous blood			Tissues.		Arterio tissue gradient mmHg.
	% saturation	O ₂ tension mm Hg.	O ₂ content vols. %	% saturation	O ₂ tension mm Hg.	O ₂ content vols %	O ₂ tension mm Hg.	vol. of O ₂ delivered.	
Normal	100	100	20	70	35	14	40	5 or 6	60
Hypoxia hypoxia	75%	45	15	40	<25	8	25	<5	20
Anaemic hypoxia	100%	100	much < 20	30	20	{ less, proportional to amount of Hb.	<20	very little	—
Stagnant hypoxia	100%	100	20	<40	<30		{ 5 or 6	<20	15
Histotoxic	100%	100	20	90	60	15	60	<5	40

Their cardiovascular and respiratory systems have been well adjusted to breathe and live in a rarefied atmosphere. The adverse effects of staying at high levels were studied by two teams of investigators, one led by Haldane in the ascent of Pike's peak in the United States and the other including Barcroft in climbing Andes in Peru in South America. Since the symptoms brought on by high altitude living were studied during expeditions to mountains, they were grouped under mountain sickness, in the beginning. All of the features of mountain sickness arise out of the fundamental cause of very much lowered partial pressure (absolute value) of oxygen in the atmosphere. The proportion of the partial pressure of oxygen in relation to total atmospheric pressure, however, may not diminish except at very high altitudes. (see 'Aviation Physiology').

The severity of the symptoms rises in proportion to the rapidity of ascent. If high altitudes are attained 'suddenly', as in a plane, which is not pressurised, unconsciousness may come on precipitously. When the ascent is slow as in mountain climbing, the first group of effects will be that of mental exhilaration. People who, by nature are quiet and reserved break out into boisterous laughter. An abnormal sense of well being (euphoria) takes hold of the affected person. Argumentativeness bordering on quarrelsomeness and even actual physical violence, may be untoward developments. Fixed ideas may be formed and foolhardy actions indulged in, to aggravate the belligerent attitude. Still later, if the ascent is continued, mental dullness supervenes. What were simple arithmetical sums formerly, now appear to be very difficult to tackle and simple mental tasks are not efficiently performed. Nausea and vomiting are seen. Muscular weakness, incoordination of movements, head ache, cyanosis, dyspnoea and a tendency to periodic respiration, are other features. Later, complete prostration may follow. The symptomatology of mountain sickness bears a close resemblance to that of drunkenness.

Nausea and vomiting may result from distension of the abdomen caused by the expansion of the intestinal gases. A tight abdominal binder is a useful preventive device. Severe ear ache due to acute difference in pressures between the two sides of the tympanic membrane, is an additional symptom. The practice of

sucking sweets by air-borne passengers, is meant to keep the Eustachian tube open in order to equalise the pressures on the two sides of the ear drum. Aeroembolism is also a possibility.

When a person continues to remain at high altitudes for long periods, certain adaptive changes take place.

1. Increased rate of breathing, reflexly caused by low oxygen tension, acting through chemoreceptors of the aortic and carotid bodies. This is the only factor which can bring about a rise in pulmonary ventilation at high altitudes.

The reflex hyperpnoea actually causes lowering of alveolar carbon dioxide content which may tend to depress the respiratory centre. Hence the lowered oxygen tension is the only protective factor, without which death will occur.

Hyperpnoea brings in its wake, alkalosis which is compensated for by increased loss of base in the urine. Hyperpnoea will cease after another important adaptive mechanism comes into operation, namely —

2. a rise in the erythrocyte count. Mountain dwellers have been observed to have a permanently raised erythrocyte count (6-8 millions) which increases the oxygen carrying capacity of blood. Even though in the lungs, individual red cells abstract much less oxygen from the alveolar air which has a lower oxygen tension than at sea level, the increase in the number of erythrocytes is intended to offset this disadvantage. A shift to the left in the oxygen dissociation curve is also seen, on account of increased affinity of the haemoglobin for oxygen. Anoxia is a potent stimulus for erythropoiesis.
3. Tachycardia, which is of short duration, may also be seen. Above 15,000 ft., the heart rate rises by as much as 20% of that at sea level.

Below a level of 10,000 ft, the respiratory and cardiovascular adjustments are adequate to ensure saturation of pulmonary

blood to an extent above 90%. At higher levels, these adjustments fail to bring about satisfactory oxygenation of pulmonary blood and that is why mountain or high altitude sickness occurs only at these levels. Natives of Peruvian Andes (13000-17000ft.) are acclimatised in one more respect - namely, at the cellular level. They can utilise oxygen more efficiently and economically than others living at less exalted places. Enzymatic changes are thought to occur and these may be genetically handed down to posterity. Such individuals can withstand the extremely low oxygen tension at heights of around 20,000 ft. and above for a few hours, whereas even experienced and veteran climbers have to breathe pure oxygen for their very survival.

One or two hazards of acrobatics in flying are considered now. When flying along a circle or loop at a high speed, if the head of the pilot or aviator, while in his usual sitting position, points away from the centre of the loop, due to centrifugal forces generated by the movement, the blood tends to be forced into the cerebral vessels. This has been termed as 'red out'. Negative 'G' is said to be the force which acts from feet towards the head. The cerebral blood vessels however, do not rupture, as the intracranial pressure also rises and supports the vessels.

On the contrary, if the head is nearer the centre of the loop than the feet, blood collects in the lower part of the body causing cerebral ischemia and sudden loss of vision and even unconsciousness. This condition is known as 'black out' and the force is named positive G, acting from head towards feet.

Caisson disease or dysbarism: Caisson is a bell-like chamber (with thick walls, but open from below) which is lowered to the river or ocean bed in order to facilitate the building of piers or supports for bridges or similar structures. A high pressure of several atmospheres is maintained inside the caisson, to keep out the water which would otherwise flood the chamber from below and hamper the work of the men in the caisson. When the workers are to be brought above the water level after their work is over for the day, they face a hazard if they are brought up rapidly from an environment of very high pressure to one of normal atmosphere. Rapid decompression causes the evolution

of nitrogen from the dissolved state (under high pressure), in the form of bubbles which may cause gas embolism and also leakage into extracellular spaces and thereby pressure on nerves and vital structures. Because of pain caused by pressure of nitrogen bubbles on sensory nerves, the joints are kept in a flexed position and this feature has given the name 'bends' to the condition. Tingling and other paraesthesiae may occur. Nitrogen dissolves under high pressure, especially in adipose tissue. When the symptoms of Caisson disease are manifested, the patient must be immediately re-subjected to a high pressure in a chamber, to redissolve the nitrogen. Subsequently, he is gradually 'decompressed' by reducing the pressure in the chamber slowly.

CARRIAGE OF CARBONDIOXIDE

Blood, as it leaves the capillaries, absorbs 4 cc of carbon dioxide (for every 100 cc of blood). Human blood holds, on an average, about 50 to 60 vol. of CO_2 in every 100 cc, arterial blood having between 5 and 10 vols. less than venous blood. Of the total quantity of CO_2 in blood, the following are the forms in which the gas occurs:

- a) CO_2 dissolved in plasma—5% (2.5 cc in 100 cc of blood)

Carbonic acid accounts for 0.1% of the gas dissolved in plasma. The solubility of CO_2 in water is greater than in plasma, on account of electrolytes in the latter fluid. The dissolved CO_2 is in equilibrium with the carbonic acid formed. Carbonic acid itself combines with the base of plasma to form bicarbonate. Thus:



- b) Part of the carbon dioxide (5%) combines with the haemoglobin to form carbaminoprotein. About a fourth of the CO_2 entering the capillary blood from the tissue cells goes to form carbaminohaemoglobin (HbCO_2). (Roughly 1cc out of 4 cc of CO_2 taken up by every 100 cc of venous blood is in the form of HHbCO_2).

- c) The major portion of blood CO_2 exists as bicarbonate of sodium in plasma and will yield — for every 100 cc of plasma — 50 to 75 vols of CO_2 , when acidified and exposed to vacuum in a Van Slyke's apparatus. This quantity is known as the alkali reserve of blood.

Whole blood, when exposed to vacuum, yields all the CO_2 held by it in the form of bicarbonate. But plasma will give up only half of the gas under the same circumstances, the remaining half being retained as simple carbonate, which needs acidification for releasing its carbon dioxide. Plasma, in contact with red cells, has been known as true plasma and it gives up all its CO_2 without need for acids to be added. A sample of true plasma is prepared from a sample of blood drawn from the arm (without exposing it to the atmosphere) by centrifuging under a layer of liquid paraffin.

Alkali reserve is meant to neutralise fixed acids produced in the body, like lactic, pyruvic, sulphuric and phosphoric acids. A reduction of the alkali reserve below 50 volumes should be called acidosis and an increase, alkalosis, according to Van Slyke. Acidaemia will imply an actual lowering of the pH of blood when alkali reserve is completely used up and alkalaemia means a rise in the pH of blood. These terms have now been replaced by newer ones and new concepts have come into vogue in this regard (not discussed here).

CO_2 exchange in the lungs occurs under the following conditions :

Lung capillary blood		Alveolar air
tension of CO_2 , mm Hg		tension of CO_2 in mm.Hg
46	————→	40

Every 100cc of blood delivers about 4 cc of CO_2 to the alveoli, under resting conditions. It is to be taken note of that the tension gradient is only 6 mm Hg, while in the case of oxygen, the difference is about 60 mm Hg. CO_2 diffuses in amounts equal to

that of oxygen, under a much smaller tension gradient because of its much greater solubility in water compared to that of oxygen.

The capillary blood takes up CO_2 in the tissues, under tensions mentioned below.

Capillary blood		Tissues
CO_2 tension		CO_2 tension
40	← ———	46 +

Here again, 4 cc of the gas enters every 100 cc of blood. One cubic centimetre of this combines with haemoglobin to form carbaminohaemoglobin, which dissociates to set free CO_2 in the lungs.

Chloride shift or Hamburger's phenomenon: The delivery of oxygen from blood to the tissues is intimately linked with the uptake of CO_2 by blood from the tissues. One cannot progress without the other taking place simultaneously.

The facility with which CO_2 enters or leaves the blood during respiratory exchanges, is due to the presence of an enzyme, carbonic anhydrase, whose special role is to accelerate the formation or breakdown of carbonic acid in the tissue capillaries and lung capillaries, respectively. This enzyme is present in blood, only in the erythrocytes and is totally absent from the plasma.

Figure 8 represents the chemical events taking place in blood, when it flows past the tissues. Because of the tension difference of 60 mms between the blood and tissues, oxyhaemoglobin gives up its oxygen, which passes to the tissues by way of the plasma (see under oxygen carriage). Oxyhaemoglobin which has been in the form of a potassium salt, KHbO_2 , now dissociates into K^+ and Hb^- , since reduced haemoglobin has less capacity to bind K^+ . Concurrent with the exit of oxygen from blood, carbon dioxide enters the blood stream. A little of it is dissolved in plasma, but a greater quantity enters the

red cells, where it forms carbonic acid at a rapid rate, under the influence of carbonic anhydrase. This acid dissociates into H^+ and HCO_3^- , the latter combining with K^+ to form potassium bicarbonate. H^+ combines with the reduced haemoglobin (Hb^-) to form HHb . Since bicarbonate ions are formed in excess in the red cell, there is a diffusion of these ions into plasma in an

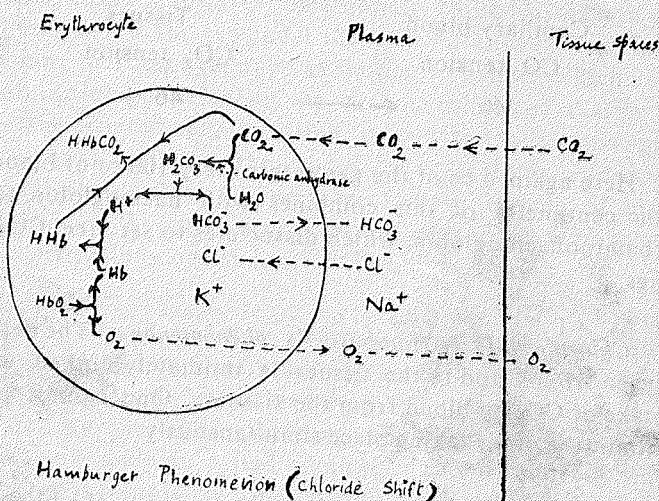


Fig. 8 Hamburger Phenomenon (Chloride Shift)

attempt to equalise bicarbonate ionic concentration between the red cell and plasma. The movement of bicarbonate towards plasma upsets the electrostatic balance and chloride ions are attracted from plasma into the red cells. This shift of chloride ions into the red cell is what is referred to as the Hamburger's phenomenon. The effects of chloride shift are:—

1. The bicarbonate content of red cells is increased.
2. The bicarbonate content of plasma is also increased.
3. The chloride content of the red cell is increased.
4. The total ionic concentration of the erythrocyte is raised and the osmotic pressure of the cell exceeds that of the plasma and water is abstracted from the plasma. The red cell is

larger in venous blood and this may increase the volume of packed cells (haematocrit value).

The above mentioned changes are all reversed when blood unloads its carbon dioxide in the lungs. Chloride shift helps the sharing by plasma of the greater buffering power of the red cells.

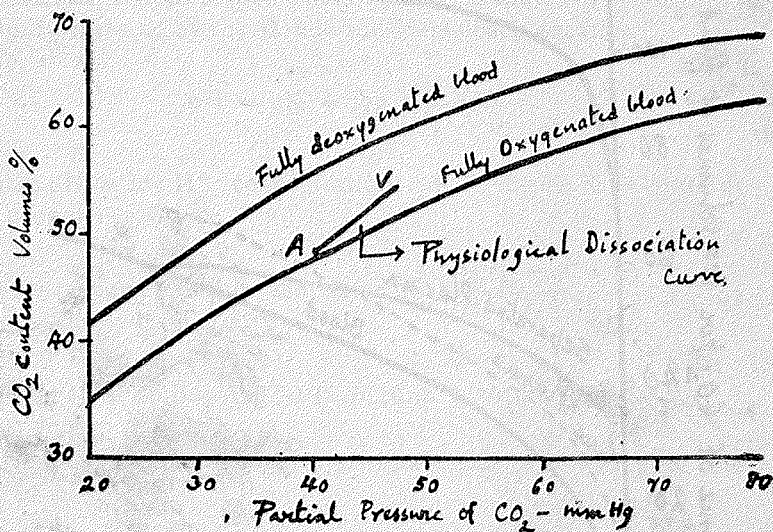


Fig. 9. Dissociation Curve of Blood (CO₂)

Fig. 9. Carbon dioxide dissociation curve: It must be stressed that the shape and position of this curve depends on the degree of saturation with oxygen of the blood. For fully reduced blood, the curve lies above and to the left of the one for fully oxygenated blood, though both arise from the origin in the graph paper. Further, the actual behaviour of blood as a carbon dioxide carrier, conforms not to the curve of either fully reduced blood or that of fully saturated blood, but to one that connects the two curves—AVB, which is known as the Physiological dissociation curve.

Point A depicts the conditions in arterial blood in which CO₂ is present in a quantity of 48 vols % and at a tension of 40 mm Hg.

Point B represents the situation in mixed venous blood which holds 52 vols% of CO_2 at 46 mms. pressure. Point B reflects the position in totally reduced blood.

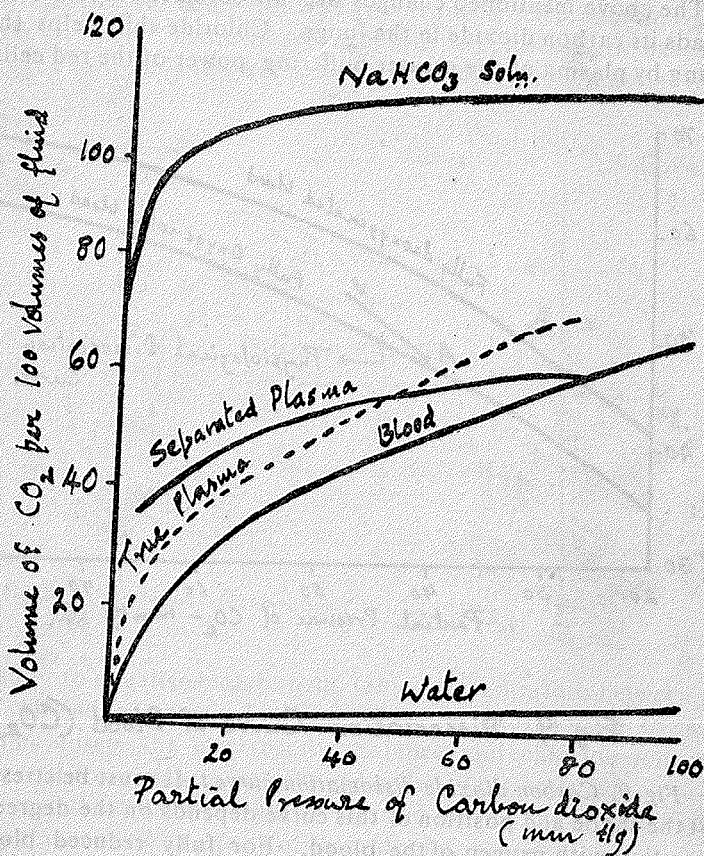


Fig 10

Fig. 10. The curves for whole blood may be compared with those of a bicarbonate solution and even with that of water. The bicarbonate solution loses only half its volume of CO_2 at zero pressure. The remaining half is retained as carbonate (CO_3). Water gives up all its dissolved gas when exposed to vacuum.

The amount of CO_2 bound to haemoglobin is also determined by the degree of oxygenation of blood. Reduced blood holds more CO_2 in the carbaminohaemoglobin form, than oxygenated blood.

The pH of blood depends mainly on the proportion between the amount of free carbonic acid and bicarbonate. This relationship is expressed by the Henderson-Hasselbach equation

$$\text{pH} = \text{pK} + \log \frac{(\text{HCO}_3^-)}{(\text{H}_2\text{CO}_3)}$$

where $\text{pH} = \log \text{H}^+$ concentration, $\text{pK} = \log K$, $K = \text{constant of proportionality}$.

Under resting conditions the value of $\frac{(\text{HCO}_3^-)}{(\text{H}_2\text{CO}_3)}$ is $\frac{20}{1}$ & $\log$

$$K = 6.10$$

$$\text{Hence pH} = 6.10 + \log 20/1 = 6.10 + 1.3010 = 7.40$$

Variations in the bicarbonate: carbonic acid ratio will alter the pH of blood.

A word is necessary about the origin of CO_2 in the tissues. In the citric acid cycle of Krebs, during one complete cycle of changes, three molecules of carbon dioxide are liberated. It is this carbon dioxide which has to be absorbed by the blood in the capillaries, to be carried to the lungs where it is lost through the expired air.

Respiratory quotient (R. Q.) : This is the ratio between the volume of carbon dioxide lost from the lungs in expired air and the quantity of oxygen taken up by the blood in the lungs from the inspired air, over an equal period. The value of R. Q. is dependent on the diet and the activity of muscles

Nature of diet	R.Q
a) purely carbohydrate	1.0
b) purely protein	0.8
c) purely fat	0.7

On a mixed diet, the R Q is usually about 0.85.

During the course of muscular exercise, the R. Q. rises up and may reach a maximum of 2.0, in the most severe form. This implies that the muscles are functioning in a state of hypoxia. After the exercise is over, it may go down below the resting value and continue so for a short while. This means CO_2 is retained in the body during this phase, to build up the alkali reserve.

THE CONTROL OF BREATHING

The activity of a living animal or man can vary from deep slumber to very strenuous exertion. Accordingly, the metabolic needs are altered. Respiration which is the means of supply of oxygen, has to be accurately modulated to be in step with the chemical processes in the body. Consequently, there is a necessity for an efficient regulation of respiration. Further, respiratory control is also directed towards maintaining, under adverse circumstances, the normal acid-base equilibrium in body fluids and keeping the body temperature constant.

This discussion is based on the well-known concept of Pitts and his colleagues, concerning the anatomy and physiology of the respiratory centres. Recent work in this field, which necessitates a drastic revision of older views, will be touched upon in a very brief manner, at the end.

The control of breathing is through the agency of a diffuse collection of nerve cells (forming part of the brain stem reticular formation) located in the pons and medulla. These nerve cells constitute three distinct entities (functional) as follows :

1. A PNEUMOTAXIC centre (PC) in the upper pons.
2. An INSPIRATORY centre (IC) in the ventral reticular formation in medulla overlying the cephalic 4/5 of the inferior olive.
3. An EXPIRATORY centre (EC) rostral, dorsal and lateral to the inspiratory centre. The inspiratory and expiratory centres overlap each other to a large extent.

These centres exist bilaterally with intimate synaptic connections between the two halves running across the midline. But the pneumotaxic centre of one side has connections only with the ipsilateral inspiratory and expiratory centres. The inspiratory centre is connected with the muscles of inspiration, by nerve fibres descending in the spinal cord and ultimately through the phrenic nerve (diaphragm) and through the spinal nerves (external intercostal muscles and other muscles). The expiratory centre is similarly connected with the expiratory muscles. Stimulation of the IC with electrodes, causes sustained contraction of the muscles of inspiration, thereby enlarging the thoracic cavity. Stimulation of the EC brings about the cessation of inspiration and the onset of expiration, but this cannot be maintained for long, as inspiratory movements break through after some time. The effects of stimulation of IC or EC probably imply that these are reciprocally innervated — i. e. — when one is activated the other is inhibited.

The work of Galen (2nd century) and Legallois and Flourens (18th century), established that the respiratory centre was in the medulla. Markwald and Lumsden (1832) further elucidated the function of the respiratory centre. The latter made sections of the brain stem at various levels, which resulted in the following effects :

1. Upto level of Inferior Colliculus — no disturbance of respiration.
2. Upper pons (pneumotaxic centre cut off) — rhythmic breathing maintained if vagi are intact — if vagi also are cut, apnoea (inspiratory spasm) occurs.
3. Through Striae Acousticae — (medullary centres cut off) breathing becomes gasping (action of primitive gasping centre may be exposed).
4. Level of Calamus Scriptorius — Respiration ceases and death ensues.

The rhythmicity of the respiratory centre is explained by Pitts in the following manner: The inspiratory centre discharges impulses to the inspiratory muscles, initiating inspiration. This causes the expansion of the lungs with stretching of the alveolar walls. The alveolar stretch receptors are stimulated and send impulses through vagal afferents to the expiratory centre which is now activated. The EC in turn sends impulses to the IC (to inhibit it) and also to the expiratory muscles, to start expiration. During expiration, as the lung is 'deflated', the tension on the alveolar walls is taken off and the stretch receptors become silent. Their afferent drive ceases and the EC becomes quiet and expiration comes to an end. The IC now resumes its activity and inspiration recommences. This mechanism is called the Hering-Breuer Reflex.

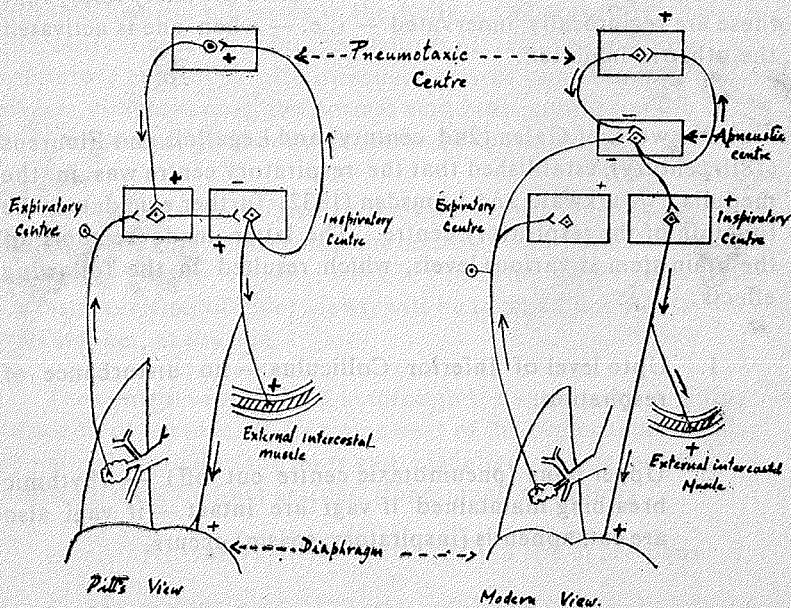


Fig. 11 The Hering-Breuer Reflex.

The pneumotaxic centre plays a role complementary to that of the vagal afferents. The IC discharges impulses not only to the inspiratory muscles, but also through collaterals, to the

pneumotaxic centre, which is now excited and sends impulses to the EC which in turn inhibits the IC and starts expiration. The PC, by itself can, even after double vagotomy, maintain rhythmical respiration, though at a slower rate and with increased depth of movements. However, the role of the PC is not as important as that of the vagal afferents. The PC assumes importance in heat polypnoea.

If both vagi are cut and the medullary respiratory centre is also isolated from the PC, prolonged inspiratory spasms occur (apneusis). The inspiratory centre is therefore under a double inhibitory influence. Its tonic discharge is interrupted by means of the two mechanisms described above and thus inspiration and expiration occur alternately.

The respiratory centre discharges its regulatory function under the influence of several factors, nervous and chemical —

Nervous factors: a) influence of higher centres.
b) reflex control.

a) Influence of higher centres: Respiratory movements are subject to limited voluntary control. Upto periods of one minute, most people can stop breathing, but spontaneous movements break through due to accumulation of CO_2 and the onset of anoxia. In certain emotional states, respiratory movements are modified as in fear, grief, surprise and hilarity (sighing, sobbing, crying, laughing etc.) In everyday activities like talking, yawning, singing, and whistling, respiration is modified so as to make the acts possible.

Experimental stimulation of certain areas of the cortex, like the superior precentral gyrus (monkey), caused increased breathing movements. Inhibition results from stimulation of lower end of inferior precentral gyrus in the cortex (monkey). But this does not mean that respiratory movements are represented in the motor area of the cortex. In man, limbic lobe (posterior orbital surface, cingulate gyrus, tip of temporal lobe, anterior temporal operculum and anterior part of insula) stimulation (during frontal leucotomy) gives rise to alterations in respiratory pattern.

- b) Reflex: 1. Hering-Breuer Reflex.
2. Chemoreceptor reflexes (carotid and aortic bodies).
 3. Presso-receptor reflexes (carotid sinus and aortic arch).
 4. Reflexes arising from other parts of body (joints, muscles, and during swallowing, defaecation, sneezing, coughing).

1. Hering-Breuer reflex: This reflex has already been described. Its importance lies in the fact that it regulates the depth of inspiration, which varies according to oxygen requirements of the body and also the CO_2 tension in arterial blood, in addition to other factors. No receptors are activated during normal expiration. Certain receptors are stimulated in forced expiration and these bring about the onset of inspiration. Thus, two sets of receptors are active in forced respiration, but only one set in quiet breathing.
2. Chemoreceptor reflexes: (for an account of the presso-receptors and chemoreceptors, see elsewhere). Changes in the chemical composition of blood bring about profound changes in pulmonary ventilation. Changes, like a fall or rise in CO_2 tension, a fall in oxygen tension and a change in hydrogen ion concentration of arterial blood, affect the chemoreceptors in the carotid and aortic bodies. Stimulation is caused by a rise in CO_2 tension or a fall in O_2 tension or a rise in acidity. Changes in opposite direction will cause depression of the chemoreceptors. The chemoreceptors, when activated, discharge impulses to the respiratory centre, through their afferent fibres (IX and X nerves) and bring about a rise in rate and depth of respiration. Absence of stimulation (or depression) causes a fall in pulmonary ventilation. Of the three factors, from the view point of survival of the animal, fall in O_2 tension (anoxia) is the most important stimulus to the chemoreceptors, but this comes into play only when O_2 tension falls to a low level—about 45 mmHg.

Even then, the change in pulmonary ventilation is not marked. Moderate increase occurs at still lower tensions (25 mmHg). The sensitivity of the chemoreceptors to O_2 lack is the sole means of protection against anoxia at high altitudes. It is the ultimum moriens of respiratory control. The chemoreceptors are less sensitive to a rise in CO_2 tension, than the cells of the RC, which are responsive to a rise in CO_2 tension by as little as 2–3 mm Hg. The chemoreceptors recognise a change only when the CO_2 tension has been raised by at least 10 mmHg. Similarly, the chemoreceptors are not very sensitive to an increase in H-ion concentration in blood, compared with the respiratory centre. Chemoreceptors are stimulated by certain drugs — lobeline, nicotine, cyanide and acetyl choline.

3. Pressoreceptor reflexes: A rise in arterial blood pressure causes depression of respiration, by stimulating pressoreceptors of the carotid sinus and aortic arch. The physiological significance of this is rather obscure. Pressoreceptors do not play a significant role in the regulation of respiration. In exercise, the inhibitory effect of a rise in B. P. on respiration is however, not evident (see elsewhere about Marey's law in exercise), probably because the chemoreceptor reflexes mask it.
4. Reflexes arising from other parts of the body: This is a motley group. During muscular exercise, impulses arising from active muscles and joints seem to stimulate the respiratory centre. In the 'second stage' of swallowing, respiration is inhibited so as to prevent the bolus from entering the glottis. In defaecation, respiration is held in the inspiratory position, to increase intra-abdominal pressure. During coughing and sneezing, respiration is modified so as to cause the expulsion of the irritant matter.

Painful stimuli arising in any part of the body will cause changes in respiration. Exposure to cold also modifies respiration. This is probably one of the means by which respiration is initiated in the newborn.

Chemical factors: The same factors to which the chemoreceptors are susceptible, exert effects on respiration also by a direct action on the respiratory centre.

Even small changes in the carbon dioxide tension in arterial blood can affect the respiratory centre. A rise by as little as 3 mm Hg is sufficient to stimulate the centre and bring about a rise in depth and rate of respiration. Rise in H-ion concentration has a similar effect. Whether CO_2 per se has an action on the centre or the greater H-ion concentration resulting from excess CO_2 is responsible for this, is a matter of dispute. Evidence is in favour of carbon dioxide itself being a specific stimulant to the respiratory centre. A fall in CO_2 tension or a lowering of the H-ion concentration, depresses the respiratory centre. It is believed that changes in CO_2 tension bring about compensatory adjustments to restore the CO_2 tension to the normal resting value of 40 mm Hg. An exposure to very high tensions of CO_2 causes depression of respiration by a direct effect on the centre.

A fall in oxygen tension in blood acts as a depressant to the respiratory centre. The greater the fall, the more profound is the depression. With complete lack of O_2 in the air breathed, unconsciousness supervenes in a very short time. It is thus seen that the reflex effects and the central effects of anoxia are opposed to each other. Severe O_2 lack tends to give rise to periodic breathing.

In parenthesis, it is to be stated that pure oxygen can be breathed for several hours without ill effects. Mixtures containing 60% oxygen can be breathed indefinitely without harm. Pure O_2 at a high pressure of 4 atmospheres, if breathed for an hour, brings about deleterious effects and this condition is termed paradoxical anoxia.

A physical factor—viz— a rise in the body temperature, as in exercise, causes changes in pulmonary ventilation. In this case, the breathing becomes rapid. In animals like the dog (no sweat glands in skin), this is an important mechanism in the dissipation of heat. This action seems to be central, i. e., directly on the respiratory centre.

In conclusion, it can be said that the effects of both nervous and chemical factors are integrated in the modulation of respiration. As Gray believes, the net effect on respiration is the algebraic sum of the effects of individual factors.

Newer concepts concerning the respiratory centres:—

In the recent past, the experiments of Hoff and Breckenridge and Wang and others have supported the view that the medullary respiratory centre is rhythmic in activity even when isolated from all chemical and afferent nervous influences. It was seen by Wang and others that a section just above the level of the medullary RC did not produce apneusis even after bilateral vagotomy. On the other hand, after double vagotomy and a division of brain stem between the upper and middle pons, apneusis occurred. Experiments employing electrical stimulation or small electrolytic lesions (by Wang et al) suggested the existence of a pontile apneustic centre in the lateral reticular formation of mid pons in addition to PC, IC and EC mentioned previously. According to these authors, the medullary centres, though inherently rhythmical in activity, were normally under the control of the pontile apneustic centre, whose tonic influence over the former was rendered intermittent by the joint inhibitory control of vagal afferents and PC.

Hoff and Breckenridge pictured apneusis as a manifestation of decerebrate rigidity, resulting from the removal of the inhibition of PC, which was included by them in the suppressor reticular system. The Hering-Brewer reflex was thought to provide the afferent drive for the suppressor system and as not important in 'breath by breath' regulation. These views have not been accepted by all.

Brodie and Borison have attempted a drastic revision of the terminology concerning the respiratory centre. Their concept of the respiratory centre is quite novel and based on considerations of functions of the various regions of the brain stem reticular formation. These ideas are yet to be accepted widely.

PERIODIC BREATHING

There are two well recognized types of periodic respiration. The better known of these two is the Cheynes-Stokes type, which is seen even in normal subjects, in special circumstances like mountain sickness and even in heavy sleep and after voluntary deep breathing. A record of this kind of respiration shows

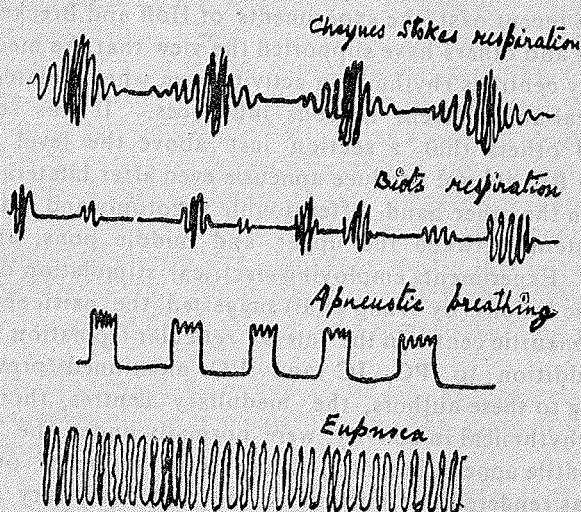


Fig.12. Normal and Abnormal types of Respiration

periods of hyperpnoea alternating with apnoea – waxing and waning rhythm. Abnormally, it is seen in extreme cardiac failure and renal failure leading to uremia, and as an effect of toxicity of respiratory depressant drugs of opium origin. Depression of the respiratory centre is held to be the cause of Cheynes-Stokes breathing. In the waning phase, because of the depression of the respiratory centre, the breathing is shallow and a fall in oxygen tension of blood occurs. This sets up reflex hyperpnoea by stimulation of chemoreceptors of carotid and aortic bodies. Increased depth of respiration (waxing) is brought about gradual-

ly. When maximum excursions of the thorax take place, carbon-dioxide tension in arterial blood is diminished as a consequence. This leads to depression of the respiratory centre, which in turn brings on the apnoeic period again.

Biot's variety is of more grave import. It signifies an adverse outcome. The alternation of apnoic periods with those of hyperpnoea is not 'regular' (if one could use this word), as in Cheyne-Stokes breathing. The duration of the two phases varies erratically. Also hyperpnoic breathing does not develop gradually with increasing amplitude, but comes on abruptly. Severe injury to the brain is the underlying cause of this condition.

WORK OF BREATHING

The respiratory muscles (those bringing about the inspiratory enlargement of the thorax) perform mechanical work which can be of the following three categories, whose total is the work of breathing.

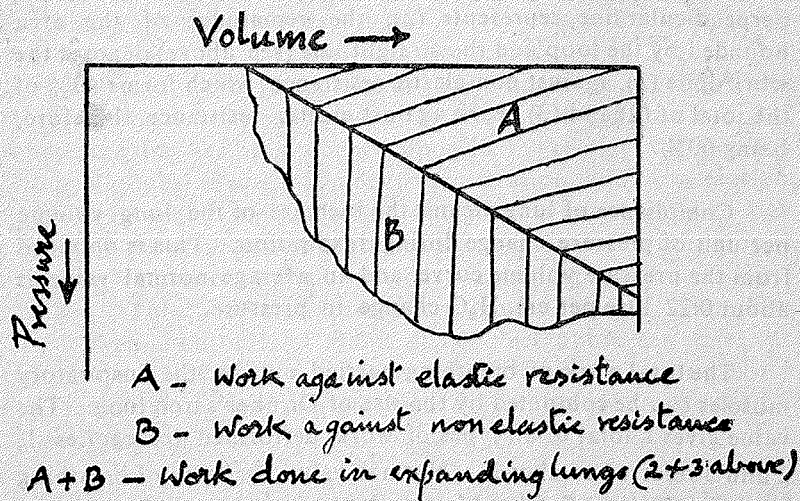


Fig. 13 Work of Breathing

1. Work performed in moving the thoracic cage—this cannot be estimated directly.

2. Work performed in overcoming the elastic resistance of the lung and bronchial tissues and thereby bringing about expansion of the lungs.
3. Work done in overcoming the non-elastic or viscous resistance by forcing air into the bronchial tree and the alveoli, against the resistance of the lung and bronchial tissues as well as the viscosity of air in the respiratory passages.

Work of (2) and (3) can be arrived at by plotting pressure volume relationships during inspiratory movement by noting the instantaneous values of the intrapleural or intraoesophageal pressures and the tidal volume. A 'loop' is obtained. The area bounded by the loop and the portion of the X-axis intercepted between the commencement of the loop and a perpendicular drawn to the X-axis from the end of the loop, gives the total work performed by way of (2) and (3) mentioned above. The triangular area bounded by the straight line joining the commencement and end of the loop, the section of the X-axis and the perpendicular line, represents (2), the remainder of the area bounded by the loop and the straight line (see above) denotes the work done (3), against non-elastic resistance which forms 40% of the total of (2) and (3), work against elastic resistance, therefore, being 60%.

Compliance of lung means the increase of the lung volume per unit of pressure change during inspiration. This is obtained from the pressure volume curve and an average normal value is about 0.22 litre per cm. H₂O change in pressure.

The total work of breathing carried out by the inspiratory muscles can be computed by the use of Drinker's iron lung. The value gives a total of all types of work performed (categories 1, 2 and 3 referred to above). Normal value for work of breathing amounts to about 0.5 kg. Metre/minute, in eupnoea. It increases five hundred-fold in maximal exercise.

AVIATION AND SPACE PHYSIOLOGY

This is a highly specialised field dealing with the peculiar problems of aviation and space exploration. While some hazards are known and measures to counteract them have been developed, yet many more dangers attendant with a sojourn in outer space have to be realised and overcome. Man or animal has evolved to live comfortably under terrestrial conditions. For a voyage into space, man needs to be adequately protected from the risks to which he may be exposed. The space ship or vehicle in which he is enclosed has to withstand the effects of cosmic factors. As far as is known now, a space traveller has to be enclosed in a chamber in order to preserve his surroundings in almost the same state as obtains on earth. A direct exposure of man's body to the celestial environment will terminate his existence in a very short span of time. Space research, as the term is understood now, is directed to enable a man to carry his own environment with him wherever he goes.

Hypoxia, high temperatures and exposure to ultraviolet light are the risks attendant with aviation at high altitudes. Of these, the first has been touched upon in the section on respiration. Inimical effects of sudden acceleration and deceleration have to be dealt with in addition, in flying at very high altitudes at which the atmospheric pressure falls to a low value, the carbon-dioxide and water vapour tensions remaining almost undiminished. Thus, the partial pressure of oxygen falls to a very low value even at altitudes of about 40,000 feet above sea level, at which the atmospheric pressure is only 100 mms. The necessity to breath pure oxygen at high altitudes is amply demonstrated by these facts.

During a very rapid ascent in a modern aeroplane, because of the cabins being pressurised, no adverse effects are seen. But, if a person were to go up in an open aircraft to a height of 50,000' in air, the gases in the hollow viscera, especially in the alimentary canal, will expand suddenly causing severe pain. But during the ascent, they may escape as flatus through the colon and also by

belching from the stomach. The air in the middle ear escape through the eustachian tube which may be caused to open by swallowing saliva. But at altitudes above 60,000', if an aviator is directly exposed to the upper atmosphere, the water in the alveoli will boil off. The body fluids also would be converted to bubbles of water vapour and the body will be completely depleted of its water by means of boiling, in about 3 minutes. Of course, death would have occurred before this.

Because of the high velocity at which modern airplanes can travel, changes in the direction of the movement will impose certain effects arising from the gravitational force. While linear acceleration (in a straight line) may not have any deleterious effects, angular acceleration can cause harm. The sharper the turn or change in the direction of movement, the more marked will be the effect. When an airplane carries out a circular movement in the form of an outside loop-the head pointing away from the centre of movement, the force acting on the subject is known as negative G tending to throw the person out of the plane. This is prevented by seat belts anchoring him down. The actual value of the force varies with the angular acceleration. In this condition, blood in the vessels is forcibly displaced towards the head and upper part of the body. Intense hyperaemia of the cranial vessels occurs and the eyes may become temporarily blind, the condition being known as 'red-out'. Fortunately, engorgement and consequent rupture of cerebral vessels are unlikely on account of the accumulation of the cerebrospinal fluid also in the head. While performing an inward loop, the force acting on the subject tends to press him down on his seat. He is said to be subjected to positive G and blood tends to collect in the lower part of the body due to the centrifugal force developed. Cerebral ischaemia is a consequence; vision suffers a black-out for a few seconds before unconsciousness supervenes. Recovery may be brought about by baroreceptor reflexes, but the afflicted person should not be subjected to angular acceleration any longer, to facilitate the return of consciousness. Bone injuries like fracture of vertebrae may occur on account of forces arising out of excessively high angular acceleration. Since the body can withstand very strong acceleratory forces applied to it perpendicular to its

long axis, a semi-recumbent or lying position is recommended while performing aerial acrobatics.

Proprioceptors in angular acceleration: It has been observed that for the efficient functioning of the maculae of utricles, the body should be leaning forwards to a slight degree. As for the semi-circular canals, unless the angular acceleration is at least 2 degrees per second, they may not signal information about the turning of the plane continuously in a circle or in a curve.

Effect of temperature variation in flying and also in space exploration: This has been referred to, under 'Regulation of body temperature'. The harmful effects of a fall in temperature as one approaches the ionosphere and the high temperatures experienced while passing through the ionosphere, are obviated by suitable engineering devices such as painting the external surface of the space capsule suitably.

Effects of rapid descent, as with parachutes: When a person jumps from an aeroplane with his parachute folded up, he rapidly gains in velocity due to the acceleratory force of gravity. Every second, the speed of descent increases by 32 feet. When the parachute opens out, there may be an appreciable tug upwards which the subject experiences as a jolt. As he lands on earth, he hits it with a force equal to the impact felt by jumping from a height of about 6 feet. Hence, the person is advised to meet the ground with the knees bent. Otherwise, fractures of the pelvis and the lower limbs may result. The parachute, as an aid to descent from high altitudes, reduces the force of impact on the ground to as little as 1/80 of that of hitting the ground without parachute.

SPACE TRAVEL

In addition to the problems of aviation, a rapid ascent into space, as in a rocket, has the undermentioned repercussions arising out of a very rapid acceleration.

Main effects seen in circulatory system :

- 1) Weight of blood and tissues increases.

- 2) Difficulty to move about (at 2.5 G acceleration) or to lift arms and legs (at 4 G acceleration), is experienced.
- 3) Blood pressure at head level is greatly reduced producing—
 - a) difficulty in breathing (also due to 2).
 - b) Loss of vision (at 4–5 G)
 - c) Loss of hearing.
 - d) Loss of consciousness (at 5–6 G).
- 4) Compensation in about 7 seconds by pressor reflexes occurs.
 - a) Heart rate increases.
 - b) Blood pressure raised to maintain cerebral blood flow.
 - c) Consciousness returns.
- 5) Acceleration at 3.5 G for 10 minutes completely disrupts circulation.
- 6) “break off” phenomenon or “Earth separation”—

Feeling of remoteness, loneliness, anxiety, exhilaration or euphoria, occur.

Anti black-out pressure Suits are worn to counter stress of acceleration and these have a pneumatic bladder system inflated to 1psi/g.

- 7) Respiratory system—
 - a) Lung compliance is reduced.
 - b) Total vital capacity is diminished.
 - c) Perfusion/Ventilation ratio falls.
 - d) Increase in arterial oxygen desaturation in the first 1–2 minutes.

Weightlessness: This is a consequence of inter-planetary travel, especially when the gravitational force of the earth is exactly counter-balanced by that of other celestial bodies. The subject has no moorings though remaining inside the space craft. To avoid the inconveniences of weightlessness, hand-holds are provided inside the space vehicle. The disposal of human wastes and the storage of food and water and hence the mode of eating (food will not stay on the plate and water will not remain in tumblers), raise problems in engineering. The physiological effects, however, are as follows:

- 1) Circulation — a) heart rate decreased
b) blood pressure slightly increased.
- 2) Nervous system — Intact vision compensates for loss of information from otoliths and proprioceptors. Otherwise, 'space sickness' results.
- 3) It has been reported that there is difficulty in swallowing, especially for solid food. Frequency of micturition and incomplete evacuation of bladder has also been seen as concomitant effects.
- 4) After prolonged weightlessness and return to earth, muscular weakness and fainting when in erect posture, are observed.

Effects of radiation in the higher atmosphere and in outer space:
The earth's atmosphere filters about 1/5th of all harmful radiations of the solar spectrum including ultraviolet light. As one ascends in the atmosphere, one is exposed more and more to lethal radiations. While flying in an aeroplane, X-rays and gamma radiations are not much important. But these assume tremendous significance in outer space.

Surrounding the earth, except in its polar parts, are certain zones or belts (Van Allen belts) of intense radiation. A passage of a few hours duration across these belts, without protection, will cause death. The radiational activity is intensified when the sun throws out flares. Theoretically, Van Allen belts can be bypassed by taking off from the earth at the polar regions and also returning to the earth in the same regions.

Effects of deceleration (during return to earth): Face becomes swollen; eyes are painful and vision is blurred; double vision may also occur. Persistent headache may arise, but this is ameliorated by bandaging the head. Choking sensation, nasal bleeding and 'Red out' (blindness with red mist) are other features.

The cardiovascular system undergoes certain changes such as — rise in arterial blood pressure in headward direction, severe venous congestion in upper part of the body, bradycardia includ-

ing a systole of short duration, nodal rhythm, absence of P-waves in ECG. Fall in arterial oxygen saturation and disturbed ventilation/perfusion ratio are also observed. Death can occur due to asphyxia following swelling up of airways and tongue.

Training of astronauts and the prophylactic use of drugs in space travel :

While it may be desirable to have inside the space craft exactly the same conditions as on earth, yet it is not really necessary. An air pressure of about 200-250 mm of Hg is quite adequate for enabling efficient respiration. This low pressure obviates the need to prevent leaks of gas from the vehicle which would otherwise be caused if high pressures are maintained (Further, oxygen need be the only gas inside the space craft). The presence of only one gas avoids the contingency of nitrogen dissolving in tissue fluids and thereby the changes of decompression sickness being caused. However, in the first orbital flight of Yuri Gagarin, the Russian Cosmonaut, the intra-cabin pressures were almost equal to that of atmosphere at sea level.

The symptoms of vertigo, nausea, headache etc, can be prevented by the use of drugs like benadryl and dramamine. The metabolic demands can also be diminished during space exploration by the use of drugs like chlorpromazine. This will entail considerable saving of food resources. The environment in a space vehicle is so adjusted that not only the harmful effects of a space journey are minimised, but in addition, the bodily requirements of oxygen and food are kept down. Thus, the subject lives in a hypodynamic state. Theoretically, hypothermia and the induction of hibernation in space travellers are desirable measures, but whether they are practicable, has to be investigated. In conclusion, it has to be said that astronauts (cosmonauts) are not trained to adapt to extra-terrestrial environment. Instead, they carry their own earthly or near-earthly environment with them. The future only can tell whether man can adapt himself to changed conditions of temperature, gravity etc. before embarking on a space tour. Prolonged isolation from fellow human beings needs suitable preliminary psychological adjustments also.

CARDIO VASCULAR SYSTEM

This system, known also as the Circulatory system, comprises the heart and the blood vessels — the arteries, the capillaries and the veins — which convey blood from the heart back to the heart. It is during the coursing of blood through the capillaries that it comes into close proximity to the tissues, though separated by the highly permeable capillary walls. It is the momentum imparted to the blood by the heart that enables the blood to flow and discharge its main function of transporting the respiratory gases, oxygen and carbon dioxide, and also its regulatory and other functions. This section is mainly concerned with how blood flow is regulated in conformity with the needs of the body.

The heart is the most important organ of the circulatory system. By virtue of its ability to propel blood through the blood vessels, it is by itself able to regulate the flow of blood to the various organs and parts of the body. However, the blood vessels, especially the arteries, have a built-in system of regulation which to a great extent is controlled by a collection of nerve cells in the medulla known conventionally as the vasomotor centre which is itself subject to various chemical and nervous influences.

PHYSIOLOGICAL ANATOMY OF THE HUMAN HEART

The heart in the human subject as well as in other mammalian forms, is a four chambered organ made up of two auricles or atria and two ventricles. A few variations of the heart like that of a fish, which has a single auricle leading on to a single ventricle and the three chambered heart of the frog wherein there are two auricles but only one ventricle, have been developed during the course of evolution. In mammalia and the birds, the heart shows right and left halves, each isolated from the other except through the pulmonary artery and its ramifications in the lungs. In order to ensure a one way flow, there are valves situated between two communicating chambers and to prevent back flow from the two large arteries (arising from the heart) at their commencement.

Thus, the tricuspid valve is situated between the right atrium and the right ventricle and the mitral (bicuspid) valve between the left atrium and the left ventricle. The aorta and the pulmonary artery are furnished with semilunar valves to prevent regurgitation of their blood content into the left and the right ventricles respectively. There are no valves as such at the entry of the great veins, the superior and the inferior vena cavae, into the right atrium.

The walls of the chambers are not all of the same thickness, those of the atria being much thinner than those of the ventricles, on account of the lesser amount of mechanical work done by the former. The walls of the two ventricles also differ in that the left ventricular wall (1.5 cms) is about three times as thick as that of the right ventricle in view of the greater pressure against which the former has to eject blood. The total volume of all the four chambers in an adult human heart is around 300 ml. and at each ventricular contraction, about 120 — 140 ml of blood are expelled, the rest remaining in the heart which is therefore never empty. The two ventricles have to eject, each, the same quantity of blood, in order to avoid complete emptying of the heart or its engorgement.

The heart is invested with pericardium which may be considered to be of two types. The outer fibrous pericardium merges at the base of the heart with the fibrous outer coat of the great vessels and at the apical region of the heart it is attached to the central tendon of the diaphragm. Thus, anchorage of the heart to the diaphragm and the prevention of dilatation of the heart are two functions subserved by the fibrous pericardium. The inner serous pericardium is itself made of two layers in the manner of the pleural and peritoneal membranes. Between the two layers is present a small quantity of thin serous fluid, acting as a lubricant as the heart contracts and relaxes.

The inner aspects of the walls of the heart chambers are covered by the endocardium which is very smooth. The valves of the heart are formed by the folding of the endocardium with some amount of connective tissue sandwiched between the

endothelial layers. The free edges of the valvular cusps are loosely tethered to the walls of the ventricles by means of the papillary muscles and the chordae tendinae which prevent the cusps from being everted into the auricular chambers, thereby making it impossible for regurgitation of blood from the ventricles into the auricles.

The muscle tissue forming the contractile organ of the heart consists of quadrilateral-shaped cells or muscle fibres which have branches establishing close contact with each other, the junctional areas presenting what are called intercalated discs—probably tendinous in nature (Fig. 5-A). The spaces enclosed by the network of the muscle fibres and their branches lodge the capillaries supplying blood to the fibres. There is no protoplasmic continuity between one cardiac muscle cell and another. The general direction of the muscle fibres is either circular or longitudinal in the auricular walls. There is a thick fibrotendinous ring separating the auricles from the ventricles. In the case of the left ventricle, muscle fibres run downwards from the fibrous ring below the auricles, obliquely towards the apex and then turn inwards to be close to the inner surface of the chambers and to end either at the papillary muscles or back again near the origin. These fibres enclose within themselves others running in a circular direction, forming a middle layer. Functionally, the entire muscle mass acts as a syncytium, so that if any part of it is excited, the rest of the muscle will be activated, the excitation spreading in all directions crossing cell borders and invading adjoining cells.

Junctional tissues: This term refers to the cells in the substance of the heart which are concerned with the initiation and conduction of the impulse necessary to activate the various parts of the heart musculature. These are the sino-atrial node, the atrio-ventricular node and the bundle of His along with the Purkinje fibres. These consist of modified cardiac muscle fibres with more sarcoplasm than the ordinary cardiac muscle fibres. Their boundaries are indistinct and their glycogen content is lesser. The conduction velocity for impulses is five times as great ($5\mu/\text{sec}$) as that of the auricular muscle fibres ($1\mu/\text{sec}$).

The sino-atrial node (S. A. node) is about 2 cms long and about 2 mms in width. It runs down from the right side of the superior venacaval opening towards that of the inferior vena cava, its external identification mark being the sulcus terminalis on the outer aspect of the right auricle. The specialised fibres forming the node are arranged in the manner of a network with nerve fibres and ganglion cells intimately mixed up. Phylogenetically, it is derived from the sinus venosus of the heart of the cold blooded animals (amphibia and reptiles).

The atrioventricular node (A. V node) is present in the inferior part of the interauricular partition or septum. Histologically, it is similar to the sino-auricular node with which it is in communication through atrial musculature.

The auriculoventricular bundle of His-Tawara originates in the atrio-ventricular node and running towards the upper part of the interventricular septum, divides into two — a right and a left branch, each of which runs down under the endocardium on either side of the septum forming a delicate network with its fine branches. At the lower end of each ventricle, this bundle turns upwards (still continuing to be under the endocardium) to reach the basal portions of the outer wall of the ventricle. Throughout its course, branches are given off to supply the more superficial cardiac muscle fibres of the ventricle. The cells of the ventricular branches and their final terminations, the Purkinje fibres, show special characteristics. They are larger, with a swollen appearance and have lightly staining nuclei in comparison with nodal cells and cells of the stem of the bundle. The entire bundle and its ramifications are completely enclosed in a covering or sheath of connective tissue and hence it is possible to display the trunk and its branches by injecting India ink into the sheath. In the mammalian heart, the bundle of His is the sole means of spread of the excitatory impulse from the auricular muscle to the various parts of the ventricle, since a direct spread from the atria to the ventricles is ruled out by the thick fibrotendinous ring separating the two sets of chambers.

Since the laboratory course in Physiology comprises several experiments on the amphibian heart, a few of its salient anatomi-

cal features are presented now. This has four chambers. The sinus venosus receives blood from the three vena cavae and in turn drains into the right atrium. The sino-atrial junction is represented by the so called white crescentic line which is in the form of an inverted V when the inferior or posterior aspect of the heart is viewed while recording the heart beat. The left auricle receives blood from the lungs. Both the auricles discharge blood into the single ventricle which thus receives both oxygenated and reduced blood. The former, however, is mainly directed to flow towards the head by means of a spiral valve in the bulbus arteriosus, which arises from the ventricle and divides into two aortae. The muscle tissue of all the chambers is continuous. There is no separation of the auricles from the ventricle by a fibrous ring as in the mammalian heart. There is no specialised or junctional tissue, the excitation process spreading along the cardiac muscle fibres themselves. One more difference is that the frog heart has no coronary vessels to supply oxygen and nutriment, both of which are abstracted directly from the blood in the chambers. Three nerve cell ganglia have been described and formerly different functions were attributed to them as follows: the Remak's ganglion situated in the sinus venosus at its junction with the right auricle was considered as strongly excitomotor; the Ludwig's ganglion is in the inter-auricular septum and is strongly inhibitory in function; the Bidder's ganglion in the auriculo-ventricular junction is weakly excitatory. It is now well established that these ganglia have no role in the initiation of the heart beat, being only ganglia of distribution of nerve fibres. The heart beat in the frog is purely myogenic in origin. This will be referred to, again, later. Other aspects of frog's heart function will be touched upon in appropriate contexts.

PROPERTIES OF THE CARDIAC MUSCLE

Structurally and functionally, the cardiac muscle fibres occupy an intermediate position between skeletal or striped muscle and plain or nonstriated muscle fibres. It is customary to consider certain properties as specific to the cardiac muscle.

1. Rhythmicity — The ability to generate impulses at regular

intervals spontaneously without an external driving force is the most striking of all the properties of the cardiac muscle. Even when the heart, be it mammalian or any other, is removed from the body and a suitable environment is provided, it can continue to beat regularly. In the case of the isolated mammalian heart, if the coronary arteries are 'perfused' under a pressure of about 5' water, with an aqueous solution of certain ions— Na^{++} , K^{+} , and Ca^{++} in the correct concentrations, with the pH adjusted to be around 7.3 by the addition of sodium bicarbonate along with glucose to provide fuel for contraction and oxygen bubbled through, the heart beat can be maintained for several hours. The amphibian heart is much less choosy and it can continue to beat for about 30 hours or more, if the fluid contains the three above mentioned ions (in a different proportion from that for the mammalian heart) and is of the same reaction as blood — sufficient sodium bicarbonate being added but without oxygen and glucose. In this case however, the chambers are perfused since there are no coronary vessels. The muscle derives oxygen directly from the external atmosphere to which it is exposed. The pressure for perfusion need be only about 2 cms.

Controversy thrived for some decades as to exactly which tissue in the heart was the source of the rhythmicity. The so-called pace maker which generates the impulse regularly to bring about the heart beat is the sinus venosus in the frog heart and its phylo-genetically later analogue, the sinoatrial node in the mammalian heart. The evidence for this is as follows:—Stannius applied a ligature (I ligature) between the sinus venosus and the auricles — the auricles and the ventricles stopped beating, while the sinus did not. Stannius put another ligature — over the auriculoventricular groove (II ligature)—the ventricle resumed its beats though at a much slower rate than the intact heart. Originally, the effects of the two ligatures were sought to be explained on the basis of the nervous origin of the heart beat (Neurogenic view). Three ganglia were assumed to play a role (see note on frog heart) in this. The first ligature injured the Remak's ganglion and so the auricles and ventricle ceased beating, in the absence of impulses reaching them, especially as they came under

the influence of the strongly inhibitory Ludwig's ganglion in the interauricular septum. The second ligature set the ventricle beating by mechanically irritating the Bidder's ganglion. But several facts accumulated subsequently and disproved this rather plausible explanation. Zig-zag cuts in the heart muscle which would interrupt all nerve fibres, did not abolish rhythmicity. Heart cells in the chick embryo exhibited regular beats even before nerve cell elements appeared near them. The apical part of the ventricle, when excised, showed beats even though no nerve fibres were present in them.

It is to be concluded from these facts that the ganglia are not responsible for the rhythmicity of the heart. The muscle tissue which is modified to take the form of the sinoatrial node in the mammalian heart and the sinus venosus in the amphibian heart, are the originators of the heart beat. The effects of the two Stannius' ligatures could be satisfactorily accounted for, on the myogenic hypothesis. The I ligature blocked the impulses from sinus venosus by means of a mechanical injury, while the II ligature excited the ventricle at its junction with the auricles. It is not practicable to perform a similar experiment on the mammalian heart in view of its anatomy (see above), but this has been done in another way. Excision of the S. A. node rendered the heart inactive. Further, warming or cooling the node accelerated the heart beat or slowed it down. When the node was excited electrically, the electrocardiogram (see further below) obtained, differed in no way from that seen in a spontaneous cardiac cycle. It was also shown that in the cardiac cycle the S. A. node was the earliest among the different parts of the heart to show depolarisation, implying that it was the first to be activated. Warming or cooling the sinus venosus of the frog's heart also effected changes in its rate, showing that it was the pace maker.

While the natural pacemaker in the human heart is the S. A. node which fixes the heart rate to be around 70/minute at rest, in certain pathological conditions, an "ectopic" focus or pace maker may arise elsewhere in the auricular muscle. The rate imposed by this abnormal pace maker is somewhat less than that due to the S. A. node. Thus, there seems to be a progres-

sively diminishing rhythmicity, as tissues farther and farther away from the S. A. node take over the role of the pacemaker in abnormal states. When the ventricles are separated from the auricles, as in the case of the Stannius ligatures or by a "complete block" in the bundle of His, the ventricles beat at a rate much less than that determined by the S.A. node — about half the natural rate. This inherent rate of the ventricle is termed the Idio-ventricular rhythm and in the human heart it is about 40/minute as seen in cases of complete heart block. When the S.A. node is in communication with the other parts of the heart, it imposes its own higher rate on the other parts of the heart which have lower rates of impulse generation. This is the reason for the sino-atrial node to be called the pace maker, as it sets the pace or rate at which the whole heart should beat.

2. *Excitability*—The ability to respond to excitation is shared by cardiac muscle with other excitable or irritable tissues. In some respects however, it differs from other types of contractile tissues.

All or None Law—Under a given set of conditions — of temperature and chemical environment—a stimulus, if it evokes a response at all from the heart muscle, will elicit the maximum response. In other words, the minimum effective stimulus will bring forth the maximum response. The minimum strength or threshold changes with time, a stronger stimulus being required with the passage of time after removal of the muscle from the body. All the same, this law is obeyed. Chemical changes may also determine the threshold strength. A fall in pH may lower the threshold. This law can be demonstrated in the frog's heart by giving single induction shocks of increasing strengths (above the threshold value), with the interval between one stimulus and the next being at least half a minute. The responses will all be of the same magnitude. While the entire mass of heart muscle behaves as a unit and conforms to the All or None Law, in the case of the skeletal muscle, only individual fibres show all or none behaviour, whereas the whole skeletal muscle as such does not.

Staircase phenomenon : When an effective stimulus is applied repeatedly, the intervals between consecutive stimuli being only

a second or two, it has been observed that the heart muscle puts forth responses of increasing degree at least for the first four or five stimuli, after which the response is of a constant size. The increasing facility of response has been termed the staircase phenomenon, since linear records (obtained on a smoked drum) of the contractions of the frog's or turtle's ventricular muscle (after applying the I Stannius' ligature), have a resemblance to a staircase. The German term for staircase, 'Treppe' was first applied to this phenomenon. The explanation for this is that when the interval between two stimuli (of same strength) is very short, the chemical and temperature changes occurring during the first response have not disappeared wholly before the next response occurs. The effects of the first response facilitate the second one. If however, the interval is much greater, the beneficial effect of the first contraction decays and is lost before the next stimulus is applied. This is the reason why, when All or None response has to be demonstrated, the interval has to be at least half a minute (see above). The frog's ventricle (after I Stannius' ligature is applied) can be used for studying this property.

Summation of sub-minimal stimuli: When the excitatory strength is below the minimum level, fast repetition of stimuli will bring about a single response with the stimulus being applied at least a few times. Each stimulus will not cause a response by itself, but the sum total of several of such stimuli, provided they follow one another very rapidly, will result in a response. The physico-chemical basis is the same as in the staircase phenomenon. The chemical and electrical alteration or 'the local excitatory state' in the muscle fibres is progressively built up with each ineffective stimulus and when the threshold state of depolarisation is reached, a response results.

Refractory period: When, on stimulation, an excitable tissue gives a response, it may not produce another response to subsequent stimulation for a short time, during which recovery processes are in progress. Such an interval of unresponsiveness is known as the Refractory period. Usually, a total absence of response may last for a short interval and is followed by one of partial responsiveness. The first stage is called the absolutely

refractory phase and the next as the relative refractory period. In the relative refractory period, much stronger stimuli will have to be employed than when the muscle was resting, prior to stimulation. The heart muscle is unique in that its absolutely refractory period lasts as long as the muscle is in a contracted state and hence it is much longer than in the case of skeletal muscle which has a very very brief absolutely refractory period. Since the cardiac muscle is completely unresponsive during the entire contraction phase, it cannot show wave summation in the graphic record of its contraction. Thus, the heart can never be tetanised like a skeletal muscle. This is as it should be, since if the heart were to go into a tetanic contraction, circulation would come to a stand-still with resulting death. The inability to indulge in a smooth sustained contraction is a built-in safeguard.

Sometimes, in certain apparently normal persons, especially smokers and in other cases which may be definitely pathological, an extra systole or premature contraction may follow a normal contraction of the heart. The premature contraction may be caused by an impulse being generated in an ectopic focus — one other than the normal pacemaker, namely the Sino atrial node. It is succeeded by a quiescent or quiet interval lasting till the next spontaneous or normal systole occurs. This quiet interval is known as the compensatory pause and its significance lies in the fact that it restores the normal rhythm of the heart action after it is disturbed by the extra systole. This period of enforced rest is due to the waiting of the heart for the arrival of the next natural cardiac stimulus from the pace-maker, after the one which arrived at the ventricle during the extra systole but was ineffective on account of the extra systole. The total duration of the normal systole before the premature contraction, the extra systole and the compensatory pause equals twice that of a normal cardiac cycle. Rarely, there may not be a compensatory pause following the extra systole, if it occurs early in the relaxation period — i. e. — immediately in the wake of the natural contraction. In this case, the cardiac rhythm is disturbed little. Such an extra systole is called an interpolated extrasystole.

Contractility—This property is shared with other types of muscle fibres. The physico-chemical basis of the contraction in the various kinds of muscles seems to be the same in all.

Conductivity — While the heart muscle can itself conduct the impulses originating in the S. A. node, yet it has a special conducting system for rapid transmission of the excitatory process. Reference has already been made to the velocities of conduction (see above). There is usually an interval of 0.12 – 0.20 sec. between the onset of the auricular systole and that of the ventricular systole. This lapse of time is accounted for by several alternate possibilities like delay of the impulse at the A. V. node, slower conduction along the auricular walls or even a latent period between the arrival of the impulse at the A. V. node and its activation. The time for spread of the excitation from the A. V. node to the farthest parts of the ventricular fibres is about 0.04 sec. The impulse spreads along the branches of the bundle of His under the endocardium, taking a U-shaped course to the ventricular parts at AV junction. At each point in the ventricle, the sub-endocardial regions are activated before the more superficial ones.

CARDIAC CYCLE

Throughout life, the heart exhibits cyclical changes in the size of its chambers, pressures developed therein, movement of blood from one chamber to another, patency of its openings, closure of the valves and electrical potentials developed as a preliminary to the contraction of its fibres. Certain sounds are also produced everytime the heart passes through the cardiac cycle. Since the changes or events that occur are of various kinds, it is convenient to describe the changes of one kind first, followed by those of others.

At rest, an adult human heart 'beats' about 70 times per minute and so an average cardiac cycle lasts for about 0.8 sec. and this value will be taken as a standard in describing the various events of a cardiac cycle. When the rate of the heart is less or more than seventy, the duration of the component events will be lengthened or shortened accordingly. Each pair of heart chambers undergoes a diminution in its size (systole), caused by the shortening of the muscle fibres in their walls, alternating with an enlargement (diastole) resulting from the relaxation of the muscle fibres. Thus we have auricular systole followed by

auricular diastole, to be repeated by a systole and diastole and so on. Similarly, the ventricles have their own systole and diastole. The two auricles contract and relax almost together and so also the ventricles, but the ventricular systole follows that of the auricles.

Auricular systole	—	0.1 sec.
Auricular diastole	—	0.7 sec.
Total	—	0.8 sec.
Ventricular systole	—	0.3 sec.
„ diastole	—	0.5 sec.
Total	—	0.8 sec.

The entire heart is relaxed for about 0.4 sec. in every cardiac cycle.

A general summary of the sequence of events in the cardiac cycle:—

Since the changes occur cyclically or repeatedly in a certain order, the description of such events can commence at any point and be continued till the starting event is once again reached. A convenient starting point would be that just before the beginning of auricular systole.—Blood has been pouring from the superior and inferior vena cavae into the right atrium and through the four pulmonary veins into the left atrium. The pressure in the two chambers is almost unchanging on account of auricular relaxation being continued. When sufficient blood has occupied the chambers, the walls begin to contract and raise the pressure. There is a short interval between the commencement of contractions of the two auricles. The left one starts its systole about 0.013 sec. later, since it has to be activated by the spread of the impulse through the right atrium. Even before the onset of the auricular contraction, blood has been flowing into the ventricle, the ventricular pressure rising and closely following that of the auricles. The auricular contraction contributes very slightly to the filling of the lower chambers. At the end of the auricular systole, there is a very short interval of 0.016 sec. before the ventricles start contracting.

As their systole commences, the pressure in these chambers rises steeply and when the intra-auricular pressure is exceeded,

the auriculo-ventricular valves close, giving rise to the I heart sound. The ventricles are closed chambers till the semilunar valves open. With further rise in the intra-ventricular pressure, which now goes above that in the aorta and the pulmonary artery, the semilunar valves open out bringing about the ejection of blood from the ventricles and causing the pulse wave in the arterial system. For some more time in the ventricular systole, pressure rises, even though blood is leaving the chamber. But soon, pressure starts to fall, even though the systole is continuing and when it falls below that in the aorta or the pulmonary artery, as the case may be, occurs, the semilunar valve closes, generating the II heart sound. Once again the ventricles are closed chambers. The auricles are in diastole. The ventricles relax and the A.V. valves open, when the pressure in the ventricles falls below that in the auricles. Blood has been flowing into the auricles from the time their systole ended. It now flows into the ventricles through the A. V. openings. Both pairs of chambers continue to relax, blood flowing into them, till it is time for the auricles to once again go into systole. Thus the cycle has been completed.

The foregoing general account of the cardiac cycle has been strung together from observations made by a number of workers studying the various aspects of the cycle. William Harvey, the pioneer worker in cardiovascular physiology, when he saw the exposed heart beating, felt bewildered at the rapidity with which the various events followed each other and wondered if any human being could ever accurately describe the cycle in detail.

Pressure changes in Cardiac Cycle : The detailed study of the cardiac cycle began with the invention of the optical manometer, by Carl Wiggers in America. This instrument consisted essentially of a glass tube of circular cross section, with one end open and the other topped by a metal tube whose upper end was closed by a rubber diaphragm. A small mirror was fixed to the diaphragm. After filling the tube with citrated saline, the open end was introduced into the particular chamber in which pressure changes were proposed to be observed. A narrow beam of light was thrown onto the mirror and the reflected ray was caught on a moving photographic film. The mirror moved like a hinged

door in and out of the tube as a result of the pressure variations developing, due to its being in communication with a heart chamber. A permanent photographic record was obtained of the pressure changes in the chamber. The record was calibrated so as to obtain the actual values of the changes in pressure. The pressure variations in all the four chambers were studied and correlated with one another to obtain a comprehensive picture.

The Intra-auricular pressure curve : A typical record of this is shown in Fig. 14.

The notable features are the three positive waves a, c and v and three negative variations x, x' & y 'a' represents the auricular systole. The rising phase upto the rounded summit is caused by the so called dynamic phase of atrial systole when progressively more and more of the muscle fibres are recruited in the contraction process with consequent rise in intra-auricular pressure. The downward course of the 'a' wave stands for the adynamic phase during which gradually the number of active muscle fibres diminishes, the pressure in the chamber falling, to reach x. The rise of the wave c is the result of ventricular contraction, the A.V. valve closing at x and the rise in the intra-ventricular pressure causes bulging of the opposed vulvular cusps into the auricle and thereby raises the pressure in the upper chamber. At c, the semilunar valve of either the aorta or the pulmonary artery opens, lowering the pressure in the auricle, which falls steeply to reach x'. The flow of blood from the great veins or pulmonary veins into the auricle, after its systole is over, continues and now tends to slowly raise the intra-auricular pressure to the point v, since the A.V. valve is closed. At v, the A.V. valve opens and the pressure once again falls till the next auricular systole commences. Occasionally, a notch or dip may be seen in the rising phase of v and this is attributed to a disturbance caused by the closure of the semilunar valve.

The two auricles give rise to almost the same features, except that the corresponding events in the left auricular curve and the right one are separated by a short interval of 0.013 sec. (see above), the former lagging behind.

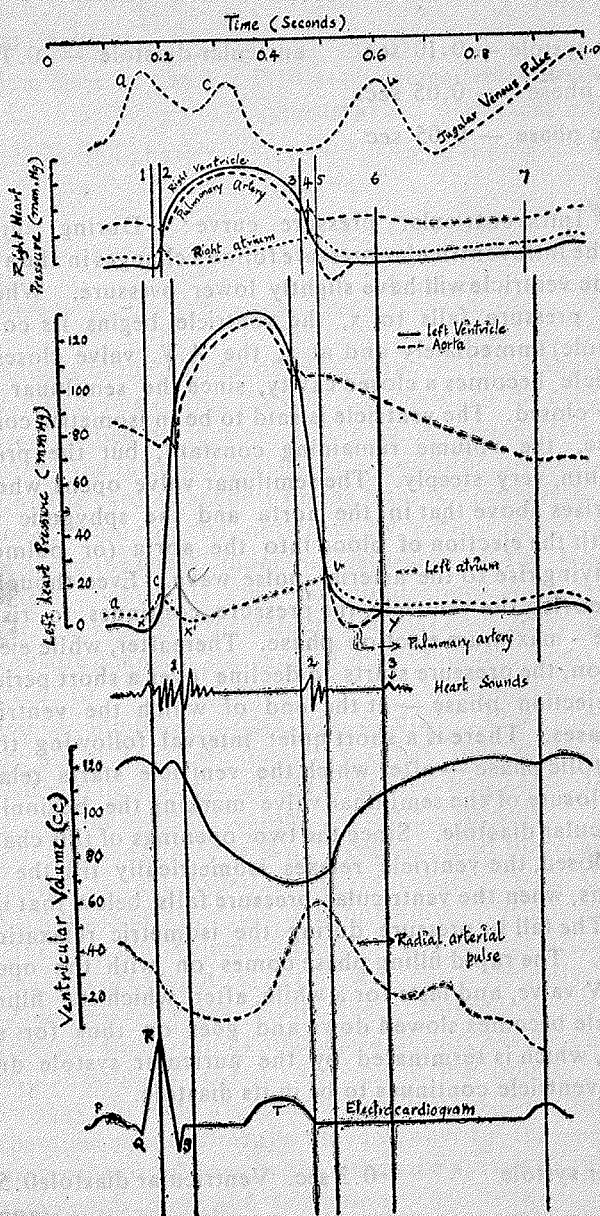


Fig. 14, The Cardiac Cycle (after Best & Taylor 1967)

auricular systole — 0.10 sec. auricular diastole — 0.70 sec.
 dynamic phase — 0.05 sec.
 adynamic phase — 0.05 sec.

The Intraventricular pressure curve: During auricular systole, the intraventricular pressure follows changes in the auricle, though the ventricle will have slightly lower pressure. When the auricular pressure falls to x , the ventricle begins its contraction (systole) immediately and at x , the A.V. valve closes and the ventricle becomes a closed cavity, since the semilunar valve is already closed. The ventricle is said to be in isometric contraction phase, the volume remaining constant, but the pressure rising within, very steeply. The semilunar valve opens when the pressure rises above that in the aorta and the sphygmic phase begins with the ejection of blood into the aorta (or pulmonary artery), giving rise to the arterial pulse wave. Even though the blood is leaving the ventricle, the pressure continues to rise for some time — maximum ejection phase. Thereafter, while ejection still goes on, the pressure starts to decline over a short period — reduced ejection phase — at the end of which the ventricular systole ceases. There is a short quiet interval following this — protodiastolic phase — after which the ventricle starts relaxing, with the closure of the semilunar valve marking the beginning of the ventricular diastole. Since the two openings of this chamber are now closed, the ventricle relaxes isometrically till the A.V. valve opens, when the ventricular pressure falls below that in the auricle. The fall in pressure during the isometric relaxation is very steep. The rapid filling phase comes on with the opening of the A. V valve, and lasts for a while, after which the filling of the ventricle becomes slowed down and goes on thus for some more time, which is terminated by the auricular systole during which the ventricle continues to be in its diastole.

Ventricular systole	0.3 sec.	Ventricular diastole	0.5 sec.
			(approx)
Isometric relaxation phase	0.04 sec.	Protodiastolic phase	
	(approx)		(approx) -0.04 sec.

Sphygmie phase

Maximum ejection phase	0.10 sec. (approx)	Isometric relaxation (approx)	-0.08 sec.
Reduced ejection phase	0.16 sec. (approx)	Rapid inflow (approx)	-0.09 sec. (approx)
		Diastasis (approx).	-0.19 sec.
		Auricular systole	-0.10 sec. (approx)

Changes in the volume of chambers - The changes in the ventricular volume during the different phases of the cardiac cycle have been studied by means of the cardiometer (Henderson's) and also by the injection of Thorotrast into the blood stream and observing the cardiac shadow on the fluoroscopic screen. Records on smoked drum can be obtained, by enclosing the ventricles after opening the chest under anaesthesia, in the Henderson's cardiometer which is in communication with a volume recorder. If however, the volume changes have to be correlated with pressure changes instead of the volume recorder being connected to the cardiometer, a Frank segment capsule is attached to obtain photographic records. One disadvantage with the use of the cardiometer is that the volume changes observed will include the muscle mass also and hence the actual variation of the chamber volume cannot be recorded. The intra-auricular volume curves have not been recorded till recently, since there were certain experimental difficulties. With the use of radio-opaque contrast media like thorotrast, it is now possible to study the auricular volume fluctuations. Consideration of this, however, has been omitted in this account. Recently, Rushmer used inductance gauges within the chambers to observe the alterations in their various diameters during systole and diastole (see cardiac output). Creese has voiced the opinion that such studies may not yield dependable conclusions, since the diameter of a chamber in one direction may not alter to the same degree as that in other directions, when either the auricle or the ventricle undergoes contraction and relaxation.

In general, the intraventricular volume curve is somewhat like a reflection or mirror image of the pressure curve, though

there are certain deviations. The ventricular volume rises slightly in the beginning of diastasis or low filling phase and thereafter it is almost constant when the auricular systole is taking place. During isometric contraction, a slight rise may precede the steep fall, the beginning of which only is seen in this phase. The opening of the semilunar valve occurs after the volume has started diminishing. The chamber becomes small very rapidly and just before the semilunar valve closes, the volume curve shows an upward trend which lasts till the middle of the isometric relaxation phase, from which moment it remains constant till this phase is over. In the earlier part of the rapid filling phase, the chamber enlarges rapidly and then more gradually, so that in the early part of the diastasis, it ceases to show any appreciable change. This state of constant volume continues till the commencement of the auricular systole.

Heart Sounds; Laennec, a French Physician (1819), was the first to devise an instrumental aid (the stethoscope) to listen to (auscultate) the heart sounds. Physicians before him, heard the heart sounds by placing their ears directly on the chest of the patient. Heart sounds give useful information about the structural and functional status of the heart and listening to them is an important step in the physical examination of the cardiovascular system.

It is pertinent to consider very briefly, the mechanism of closure of cardiac valves in this connection, since heart sounds are, in the main, considered to be generated by valvular closure.

Closure of valves of the heart: The current ideas with regard to the mechanism of valve closure, arose chiefly from the work of Henderson, Johnson and Dean. The valvular cusps of the auriculo-ventricular valve are thought to be brought into apposition due to the sudden cessation of flow of blood from the auricle into the ventricle, when ventricular systole commences. The arrest of downward flow creates a negative pressure in the auricle and this is thought, by the above mentioned workers, as being responsible for the valvular closure. Eddy currents formed under the valve cusps also aid in the closure. Eversion of the

cusps into the auricles as the intraventricular pressure rises, is prevented by simultaneous contraction of the papillary muscles during ventricular systole.

The semilunar valve is formed by three cup-like cusps whose free margins come into contact, forming a Y-shaped line when the valve is closed. When ventricular systole comes to an end, blood in the aorta tends to return to the ventricle. This causes effective closure of the valve by filling of the cusps by blood.

Two "classical" cardiac sounds are heard when the chest is auscultated over the precordium. Occasionally, another sound may also be heard by keen listeners. For clinical purposes, the two sounds which are always heard, are the only ones that matter and these can give reliable information, most often, of the state of the heart as a pumping organ. Nowadays, it is possible to obtain permanent records of the heart sounds either on the tape recorder or graphically with the use of a phonocardiograph. A fourth 'sound', if it can be so called (it is never heard by the ear), may be present in graphic records along with the first second and the third sounds. A number of people can simultaneously hear the heart sounds through the aid of a cardiophone. Stethoscopes are now available with one chest piece or bell connected to a large number of ear pieces, through which several individuals can hear the sounds. This is a useful aid in clinical teaching.

The classical heart sounds designated I sound and II sound, are commonly represented by the syllables Lub and Dup respectively.

I sound — The closure of the auriculo-ventricular valves is the main factor in the causation of this sound. When the valvular cusps (valvular element) are brought to apposition, they, along with the chordae tendinae, are put under tension and hence vibrate. Contribution to the intensity of this sound comes also from the vibration of the blood column impinging on the walls of the aorta and the pulmonary artery (vascular element) and to some extent by the contraction of the ventricular muscle (muscular element). This sound appears 0.008 sec. before the spike of the

R-wave of the electrocardiogram and lasts for about 0.18 sec. These measurements have been obtained from records, using a phonocardiograph. Since both the A. V valves contribute to this sound, the two components are known as the mitral and tricuspid sounds. The former is best heard at the 'apex beat' area - $3\frac{1}{2}$ " lateral to the midsternal line in the 5th left intercostal space. The tricuspid sound is clearly heard at the lower end of the sternum. The first sound is longer in duration, lower in pitch and louder, than the second.

II sound — This again consists of two components — the aortic and the pulmonary. Immediately after the two semilunar valves close vibrations occur in the blood column and the walls of the aorta and the pulmonary artery, because of the stretching of the valvular cusps. In a graphical record, the commencement of this sound is about 0.10 sec. after the highest point in the T-wave of the electrocardiogram and the duration is about 0.10 sec. The aortic sound is most clear and intense over the second right costal cartilage and the pulmonary sound in the second left intercostal space near the sternal margin. It has to be emphasized that though each sound or one of its components is maximally heard over one part of the precordium, other sounds are also heard there, though not with equal facility. These areas however, do not lie opposite the valves which are responsible for the sounds.

The intensity of the first sound is dependent on the force of ventricular contraction, while that of the second sound is related to the height of the arterial pressure. These facts have been adequately established by the work of Carl Wiggers.

The causation of the third sound is a matter of controversy—some ascribing it to the asynchronous closure of the two semilunar valves, the sound arising from the delayed closure of one of the valves being assumed to be the third sound. Others doubt this in view of the long interval between the second and third sounds. Alternatively, the opening snap of the A. V valves is thought to be responsible for this. Clinically, it may not be of any importance and the student need not pay any attention to this, till more is known regarding this sound. Even "after-vibrations" of the aortic valve have been considered as a possibility but the same objection as in the first case holds good again.

THE ELECTROCARDIOGRAM

Nervous and muscle tissues show electrical activity when excited. This aspect has been considered in detail under the physiology of the nerve fibre, to which reference may be made. A muscle fibre, be it of the skeletal or the cardiac type, like the nerve fibre, exhibits a resting "membrane potential" while inactive. This is to say that there is a potential difference of about 70mV. between the inside (negative) and the outside (positive) of the fibre. The electrical membrane which is not visible under the ordinary light microscope, maintains the potential difference because of its high impermeability to cations like Na^+ and K^+ . On excitation, the potential difference gets not only abolished (depolarised), but also reversed with the inner aspect becoming positive, for a very short while. If two electrodes are placed one on the outside of a resting muscle fibre and the other on the exterior of an activated fibre and both connected to a sensitive recording device, a potential difference is observed. When the cardiac impulse spreads out from the S. A. node, successively different portions of the heart get depolarised and later regain the resting polarised state. Potential differences can be recorded at any moment in a cardiac cycle, between a resting polarised part of the heart muscle and a depolarised segment. In the course of the cardiac cycle, what was resting a moment back may become activated the next instant and vice versa. Since the depolarisation wave sweeps over the entire heart muscle, it may not be informative to record potential differences between any two chosen spots on the surface of the heart itself in order to get an overall conception of the cardiac cycle.

The heart is surrounded by extracellular fluid (a few cubic centimeters of pericardial fluid also) and other organs whose cells are also bathed in extracellular fluid. In other words, the heart is placed in a volume conductor, the fluid acting as a conveyer of currents to the body surface. Currents generated at any moment in the cardiac cycle between the large polarised part and the small depolarised one, as the cardiac impulse travels from the pace maker to reach every other part of the heart muscle, can be recorded continuously by electrodes placed on the skin (electrical contact obtained with an electrolyte jelly).

From the physical theory developed to account for the occurrence of the potentials, it has been deduced that the size and direction of the potential change (positivity or negativity) depends on the magnitude of the solid angle subtended by the wave front (the boundary separating the depolarised zone from the inactive parts of the muscle) consisting of innumerable dipoles, at the electrode. A dipole is formed of a pair of positive and negative charges placed close together. When the wavefront moves away from the electrode, negative potentials are recorded and when it approaches the electrode, positivity will result at the electrode. (see further below about the main positive and negative deflections of the ECG).

Einthoven was the pioneer in recording the electrocardiogram. He firmly established the principles of electrocardiography with its underlying physical and mathematical basis and also invented a sensitive recording device the string galvanometer, which has not only great sensitivity but also very little inertia, making it an ideal instrument for faithfully recording the very rapid and minute electrical changes in the heart. Subsequent to this, other instruments which are of the direct writing type, have been developed and most of routine electrocardiography is performed using these robust and portable machines. The cathode-ray oscilloscope is admirably suited for this purpose, as it has high sensitivity and absolutely no inertia. However, this is not so widely put into use, in view of its lack of portability and the necessity to photograph the oscilloscope screen for obtaining records.

Certain standard locations on the body surface have been chosen to record these currents in order that normal patterns of electrical activity of the heart could be established for purposes of study. Since potentials have to be recorded by using two electrodes placed wide apart on the body, initially three pairs of bipolar leads were chosen as indicated below. A graphic record of the electrical currents generated by the beating heart has come to be known as the electrocardiogram (ECG) and the instrument or recording device as the electrocardiograph.

- I lead — Left arm and right arm
- II lead — Right arm and left leg
- III lead — Left leg and left arm.

The electrode need only be placed on the corresponding shoulder in the case of the arm or symphysis pubis in the case of the leg, as required by the principles of volume conduction. Since it is not easy to strap electrodes in place on the shoulder or over the pelvic region, electrodes are placed conventionally on the ventral aspects of the forearm and the medial aspect of the leg concerned, taking for granted that the arms act as linear conductors in that the entire length of the limb is at the same potential. As far as the legs are concerned, it does not matter much whether the right leg or the left is chosen for placing the electrode. But somehow, the left leg has come to be preferred to the right leg. The electrocardiograph is so constructed that in the graphic record obtained, upward deflections will mean that in the first lead, the left arm is positive in relation to the right arm, in the second lead, the left leg is positive with respect to the right arm and in the third lead again the left leg is positive while the left arm is negative.

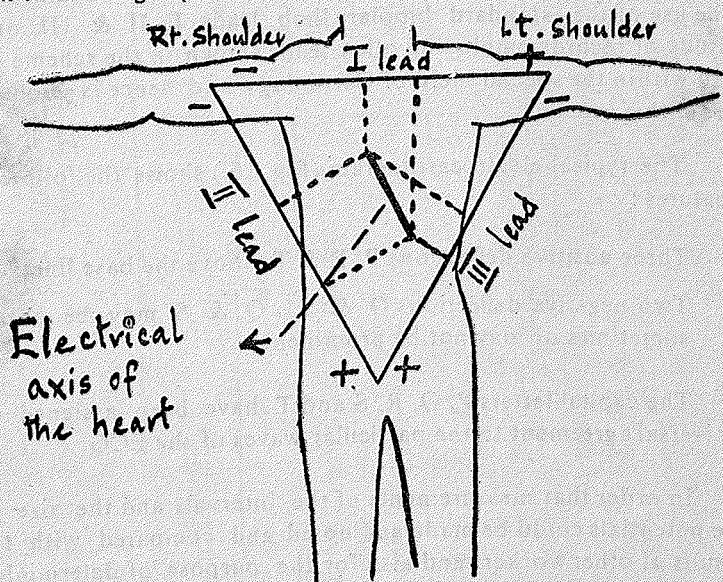


Fig 15 The Standard Limb Leads with Einthoven's Trianale

Much of the earlier work was conducted employing the three standard bipolar limb leads as the above-mentioned ones have come to be known. Later, other leads have been used. Still later, what have come to be known as unipolar leads (a term not quite correct) have come into vogue. Oesophageal leads are a new development. The term unipolar lead is misleading because actually, there are two leads since there should always be two leads to tap potentials. Unipolar lead refers to the electrode (recording electrode) placed on the precordium or near it, the other electrode (indifferent electrode) being far away from the heart and hence considered to be at zero potential. The ECG is assumed to show only changes below the recording electrode. The scheme (P. 179) gives all the leads evolved since Einthoven's time.

The description of the normal ECG will be of that obtained by the use of the standard bipolar limb leads I, II & III only. Study of records employing other leads shown in the scheme will fall within the special field of Cardiology and hence is excluded from this account.

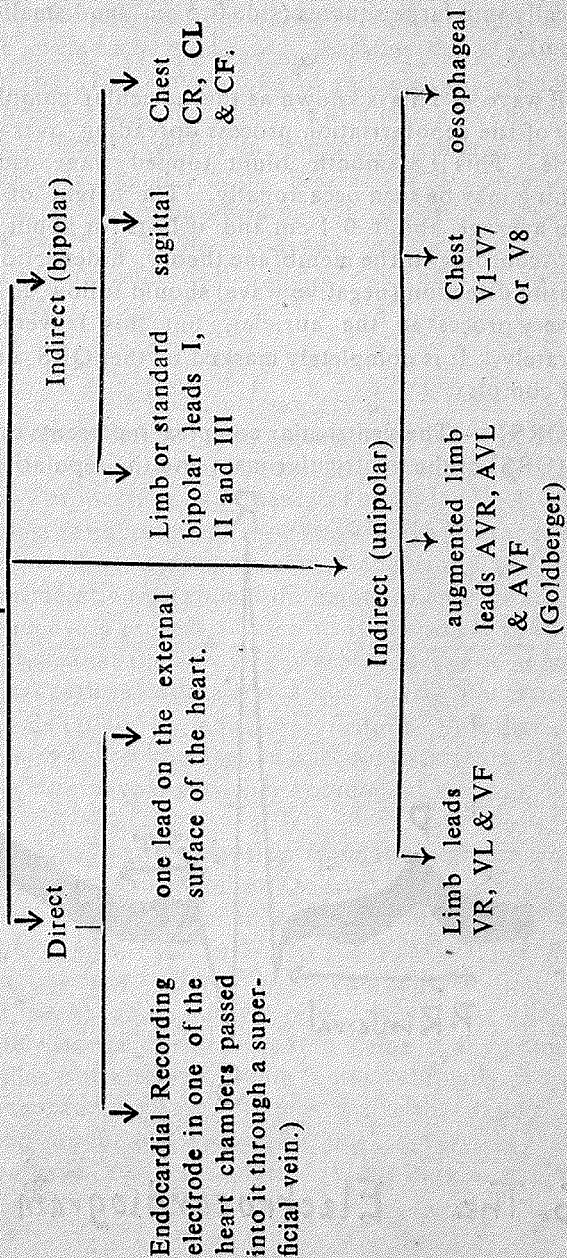
The typical electrocardiogram (Fig. 16) shows the following features :

1. Three positive deflections P, R & T (above the base line)
2. Two negative deflections Q & S. Q & S may be absent sometimes or may not be prominent.

The capital letters P, Q, R, S and T have been assigned by universal agreement to the particular waves of the ECG.

In order that measurements of the intervals and the size of the potentials could be made and noted and compared with the results of other workers and also for the purpose of determining the normals, the speed of movement of the recording paper and the 'gain' (deflection per unit potential change) have been standardised. The paper moves at the rate of 25mm/sec. and for each mV potential change, the lever moves up or down by a centimetre. Individual features can be minutely examined if desired, by having higher speed 50 mm/sec. and higher gain

ECG Leads



(2 cms/mV). The ECG paper is ruled both horizontally and vertically into large squares (side 0.5 cm) and smaller ones (side 0.1 cm).

P wave — This is known as the auricular complex and is the result of the depolarisation process spreading over the auricular muscle. This is a smooth blunt topped wave usually, though notching may be seen occasionally. The height of the wave is on an average, about 0.1 cm and it lasts for about 0.10 sec. or so. According to the membrane theory, a deflection, T_a , in the opposite direction (negative wave) should follow, to represent the recovery process in the auricles, but this is very rarely seen separately. It is completely masked by the QRS or the ventricular complex.

QRST — The ventricular complex represents the depolarisation (QRS) of the ventricular mass and the repolarisation process

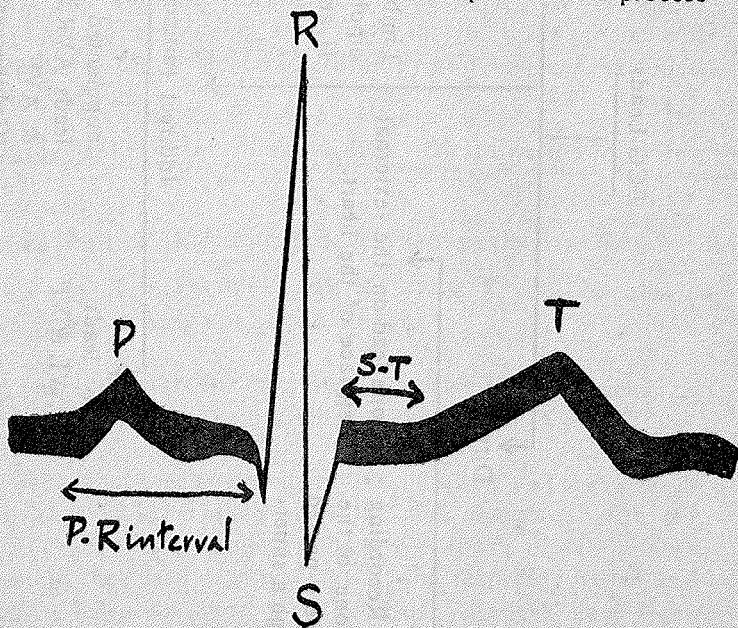


Fig 16. The Electrocardiogram II lead

(T). The small downward notch Q is not always present. It is thought to be due to the impulse coursing down the interventricular septum. The R-wave is the tallest of all and is usually upward, in direction in all the leads. Occasionally, it may point downwards in lead III. Any splintering of the R-wave seen in all the leads at the same time, is indicative of a lesion in the ventricular muscle. The R-wave has an amplitude ranging between 0.7 and 1.7 mV. The heights of the R-wave in the three leads conform to a certain relationship, which is expressed as Einthoven's Law "the height of R-wave in the second lead is equal to the algebraic sum of the heights of the R-wave in the I and III leads".

$$R_{II} = R_I + R_{III}$$

This relationship can be proved geometrically. The R-wave precedes the rise in the ventricular pressure by about 0.02 sec. The S-wave may or may not be present. The entire QRS group of deflections last for about 0.1 sec. The T-wave (average height 0.29 mV) is caused by the repolarisation of the ventricles. From theoretical considerations, it should lie below the base line, as it represents the recovery process. Since it is not so, it stands to reason to conclude that the recovery process does not take the same anatomical pathway as the activation wave. Inversion of the T-wave is definitely an abnormal feature. Another wave designated U may follow the T-wave but not invariably. This is seen in athletes who have high stroke volume.

P-R interval: The time elapsing from the beginning of the P-wave to the commencement of the Q-wave or, in its absence, the R-wave, is a measure of the time taken for the excitation process to travel from the pacemaker to the proximal part of the interventricular partition. Formerly, it was believed that there was a delay at the AV node, but it is now known that the conduction is merely slowed down without a delay at any point. It seems to lengthen out with age, within limits. Normally, it ranges between 0.12 sec. and 0.20 sec. Values above the higher limit indicate delayed conduction, as in heart block. Very very rarely, the P-R interval may be very short. (Wolff-Parkinson White syndrome)

S.-T. segment — The ECG lies close to the base line or on it during the interval between the S and T waves and hence it is known as the iso-electric interval during which the entire ventricular musculature is in a state of depolarisation and no potential difference can be recorded between any one part of the ventricles and any other. It has also been noted that this period coincides with the maximum ejection phase of the ventricular systole. Q-T interval gives the time of ventricular systole.

It must be emphasized at this juncture that all electrical events as seen in the ECG, precede the corresponding mechanical events. Thus, the P-wave and the QRS complex occur before auricular systole and ventricular systole actually take place. Further, the heights of these deflections bear no relationship to the force of contraction of the auricles and the ventricles.

Electrical axis of the heart : As mentioned before, the excitation wave moves away from the S. A node towards the ventricles and the main direction of its movement changes from instant to instant. Also, the resultant of the large number of dipoles forming the wave front changes in magnitude. The direction and the force of the resultant at any moment will represent the instantaneous electrical axis or vector of the heart. During the cardiac cycle, the direction and magnitude of the vector also changes in a cyclical way and the line joining the ends of the innumerable vectors will form an irregular loop disposed in a three dimensional space. This has been called the vectorcardiogram whose projection in any one of the planes — frontal, sagittal or transverse, can be seen on the oscilloscope screen. Vectorcardiography is a very specialised form of electrocardiography.

Einthoven's triangle — The three standard limb leads are taken to form the sides of an equal sided triangle. The position and length (force) of the electrical axis at any moment in the cardiac cycle can be geometrically worked out, knowing the size of the potentials developed in at least two of the standard limb leads. These potentials are marked off on the corresponding sides of the triangle. Perpendiculars (verticals) are raised at the ends of the portions (representing the potential values) on the two sides of the triangle. These perpendiculars

intersect each other at two points inside the triangle. The line joining the points of intersection will represent the instantaneous vector, both in direction and magnitude of force. Einthoven's law (see above) can be proved by means of this triangle.

The electrocardiogram has become an indispensable aid to cardiac diagnosis since portable machines were developed. All the same, it should be borne in mind that it is not a substitute for physical examination of the heart. On the other hand, one could obtain much useful information from the ECG, such as the rate of the heart and the rhythm of the heart. The detailed interpretation of the ECG, though it falls within the purview of the specialist, need not deter even a general physician from attempting it. However, a casual approach is to be deplored. There is no substitute for experience in this field and great caution is to be exercised in correlating the features of the electrocardiogram with the underlying pathological lesions. Abnormal electrocardiograms have been excluded from the scope of this account.

CORONARY CIRCULATION

The arteries and veins of the coronary system of vessels surround the heart in the form of a wreath and hence its name. Unlike the frog's heart which derives its oxygen and nutriment directly from the blood in the chambers, the mammalian heart has an elaborate system of arterial vessels as well as venous channels. The two coronary arteries, right and left, arise as ostia or openings in bulge-like formations, in the walls of the aorta, known as the sinuses of Valsalva. But for these sinuses, the coronary opening in the aorta would be closed by the cusps of the aortic semilunar valves.

The left coronary artery is a short one running to the upper end of the anterior interventricular groove where it divides into two branches, the left circumflex and the interventricular, the latter running down the interventricular groove. The right coronary artery runs forward between the pulmonary artery and the right auricular appendix, to the coronary sulcus and then downwards to reach the right extremity of the inferior cardiac margin.

It then curves to the left in the coronary sulcus to reach the posterior end of the inferior interventricular groove where the interventricular branch is given off. This branch runs forward in the inferior interventricular groove to the apex where it anastomoses with the corresponding branch of the left coronary artery. The right coronary artery, after giving off its principal branch (interventricular), ends by anastomosing with the circumflex branch of the left coronary artery. In 50% of human subjects, the right coronary artery supplies most of the blood to the heart. In 30% of people, the right and left arteries contribute equal shares. In 20% of subjects, the left artery is the predominant one and this last group is most susceptible to coronary thrombosis and its attendant serious or even fatal outcome.

Venous drainage: The venous vessels are of two kinds—superficial and deep. The superficial system comprises the following. The coronary sinus in the coronary sulcus opens into the right atrium in its posterior part behind the auriculoventricular orifice. It drains most of the blood derived through the left coronary artery and 70% of the total coronary arterial flow. The great cardiac vein ascends along the anterior interventricular groove along the I.V. branch of the left coronary artery and empties into the coronary sinus. The anterior cardiac veins are seen on the surface of the right ventricle and empty themselves directly into the right atrium.

The deep veins are in the myocardium and drain blood into the chambers of the heart by means of Thebesian and other vessels. The capillary plexus is very rich and the heart muscle receives more blood, weight for weight, than the skeletal muscle.

The question of collateral circulation looms large in a discussion on coronary circulation, in view of the importance of coronary occlusion as a major killer-disease. The chances of survival depend on the rapidity with which collateral circulation can be established so as to supply blood to the ischaemic tissues. When a major artery or its branch is suddenly occluded, death may supervene before collateral channels can open up sufficiently widely to maintain the viability of the affected part of the heart

muscle. There are a few possibilities as regards collateral circulation in the heart.

1. Potential anastomotic channels exist between vessels ranging in diameter between 50 and 100 microns. These develop into actual connections when a larger vessel is closed, provided sufficient time is allowed.
2. Thebesian vessels do not serve as alternate channels for arterial blood supply even though some of them open into the left ventricle. Only by retrograde flow (from the chamber of the ventricle back into the vessel) can they serve to act as collaterals.
3. Arteriosinusoidal and arterioluminal vessels provide communication between coronary arteries and the ventricles. It is not known if these have any functional importance.
4. Extra cardiac connections have been seen between auricular arterial twigs and direct branches of aorta and internal mammary arterial branches like pericardial, bronchial, phrenic and oesophageal arteries.

The cardiac muscle receives about 225 ml of blood every minute, this amounting to 4-5 % of the cardiac output. It extracts about $\frac{3}{4}$ of the oxygen content of blood — i. e. — the coronary venous blood contains 4-5 vols. %. This uptake of oxygen is not increased even under stress. This works out to 8-10 mls. of O_2 per 100 gms of weight of the left ventricular mass. In systole, the oxygen utilisation is about three times that in diastole. Contrary to older ideas, the heart muscle can incur an oxygen debt, though not to the same extent as skeletal muscle. In what is known as reactive hyperemia, the oxygen debt is not only cleared completely but even overpaid, unlike in other tissues. At the height of muscular exercise, the work load of the heart is increased 14 times but the coronary arterial flow rises by only 5-7 times. Therefore it is concluded that the mechanical efficiency of the heart increases.

Regulation of blood flow through the coronary system: Three factors are involved in this. 1) Driving force — arterial pressure 2) Vasomotor tone. 3) Compressive force around the arteries by the heart muscle during systole. Factors 2 & 3 appear to be more important than (1). In the left coronary artery, blood flows throughout the cardiac cycle except in the early systole. The blood flow is however, much less in systole than in diastole. The flow in the right coronary artery follows that of the aorta, more or less. The flow in the coronary sinus and other venous channels rises and falls steadily. Systolic flow in left coronary artery ranges between 15-60% of the diastolic flow. In stress states, coronary arterial flow rises by 300-400% the Systolic flow bearing the same ratio, as at rest, to the diastolic flow or equalising it or even exceeding it. Thus, systolic flow is highly variable and depends on force of cardiac contraction. Pressure in the left coronary artery varies from about 20 mmHg during diastolic, to 80 mmHg in systole. The direction of flow in the larger arteries of the heart (intramural flow) may even be reversed during the early part of systole, on account of compression exerted by the contracting heart muscle. In the capillaries and veins, the flow is in the normal direction. The nett capillary flow (volume of blood per unit time, leaving the coronary system) varies according to the phases of the cardiac cycle. The changes are much more marked in the left coronary artery than in the right one, since the former is subjected to the greater pressures exerted by the left ventricular muscle. The curves depicting coronary flow have been plotted, making use of data obtained from animal experiments. The following description refers to the left coronary artery. The flow in this vessel falls to a very low level after the initial third of the ventricular systole on account of strong compression of the intramural branches of this vessel. As the pressure on the vessels falls from now on, in the mid part of the systole, there is a rise in the flow, which however, is not sustained till the last part of the systole when, by reason of diminished force of contraction, the flow rate falls once again, though not as low as before. As the diastole comes on, the flow rate increases steeply in its early part and more gradually later on, to reach a rounded and somewhat sustained maximum. Towards the fag end of diastole, the flow once again tends to decrease, this trend continuing into systole. The fluctuations in the flow in the right coronary artery

are not so marked, in view of the poor vigour with which the right ventricular muscle contracts.

The role of autonomic nerves in the control of coronary flow is not fully understood. Stimulation of the parasympathetic fibres of the vagus causes not coronary vasodilatation, as one would expect, but vasoconstriction. Likewise, sympathetic stimulation brings about vasodilatation. These effects are pre-

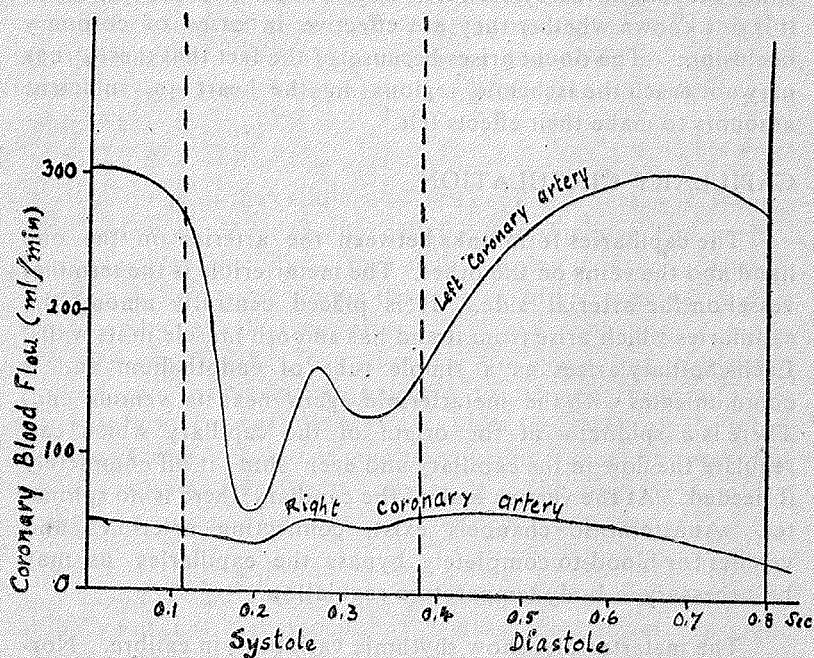


Fig. 17 The Coronary Circulation

sumed to be the indirect result of the action of these autonomic nerves on the cardiac musculature. Sympathetic excitation causes increase in the rate and force of cardiac contraction leading on to the release of vasodilating substance like CO_2 , adenosine phosphate etc. (into the extracellular fluids) which are responsible for the dilatation of the coronary arteries. A similar expla-

nation applies to the vasoconstriction resulting from parasympathetic stimulation. The increased flow of blood caused by sympathetic stimulation is known as reactive hyperaemia, since it is caused by metabolites. Part of this effect may be due to the milking action on the blood vessels by the contraction of surrounding muscle fibres.

Certain vasodilator drugs like nitrites, xanthines and others cause vasodilatation by a direct action on blood vessels. Even so, it is not known whether they are effective in cases of coronary occlusion. The doubt arises because of the fact that these drugs may not reach the ischemic regions in the heart in sufficient amounts to make their effects felt.

CAPILLARY CIRCULATION

The capillaries form links between the arteries on the one hand and the veins on the other. The metarteriole is the terminal vessel on the arterial side. It is placed centrally among the capillaries which arise from it and has smooth muscle in its walls. Each capillary arises as a simple tube of endothelium and it communicates with the metarteriole again near its venous end. There is a sphincter at the origin of the capillary which can regulate the flow in the capillary and even shut it off completely if needed. At the venous end of the capillary, there is no sphincter. Anastomotic channels exist, connecting arterioles and venules for blood to completely bypass the capillaries as may be necessary in body temperature regulation.

The metarterioles show rhythmic variations in calibre. Normally, the precapillary sphincters are in a state of contraction and very few capillaries may be patent. When the same tissues become active, more capillaries are opened out by the relaxation of the sphincters. This effect seems to be due to local factors — mechanical irritation and chemical agents like adrenaline and histamine. The capillary flow may rise several hundred-fold from the resting state to that of intense activity. Adrenaline $1/10,000,000$ produces constriction, but in higher concentrations ($1/8000$) causes dilatation. The regulation of capillary blood flow is through the agency of the precapillary sphincter and this is independent of the arteriolar mechanisms. According to Sir

Thomas Lewis, a pioneer worker in this field, all capillaries are open always but they dilate to allow more blood during activity. These vessels are very tiny, being only about $\frac{1}{2}$ to 1 mm. in length and of inner diameter — 7μ or more. Some of these minute vessels are not wide enough to allow the red cells to pass through them. Only plasma flows in these and the separation of plasma from the cells is known as skimming of plasma. The total cross section of all the capillaries laid side by side, is said to be about 700 times that of the aorta and this is the reason why intracapillary pressure is so low as compared to the intra-aortic pressure, even though the flow velocity is very low in the capillaries.

Histology of the capillary — The capillary vessel is formed of a single layer of endothelial cells 0.5μ in thickness and covered by connective tissue fibrils from neighbouring connective tissue. The cement substance joining the cells is often renewed and is produced by the cells themselves. Calcium ions and high pH are necessary for the formation of the cementing substance. Protein from the plasma is believed to be adsorbed onto the inner surface of the capillary and it closes the pores of the inter-cellular cement. Saline or gum transfusion washes it away but serum or plasma transfusion restores it. The opening up of the pores, as by a saline transfusion, may lead to oedema.

Capillary permeability — Gaseous, fluid and electrolyte exchange occurs across capillary walls. Leucocytes cross the capillary barriers by a process called diapedesis. The total capillary surface available for these transfers amounts to 6300 sq. metres (68,000 sq. ft.) — equivalent to a strip 12 miles long and 1 foot wide. When rolled, this would be only of the thickness of a lead pencil. Capillary dilatation favours filtration, whereas capillary constriction promotes reabsorption. Permeability depends on the state of the cementing substance. Protein, normally cannot pass to the extracapillary spaces. Capillary permeability is reduced by adrenal corticoids, calcium ions and a rise in pH. It is increased by histamine, tissue extracts, fall in pH and warmth. Anoxia and lack of vitamin C cause capillary damage.

The cementing substance may be hyaluronic acid. This is dissolved away by hyaluronidase.

Certain cells known as Rouget cells surround the capillaries at intervals. It is possible that they may alter the diameter of the capillaries: These are of reticuloendothelial origin.

Innervation of Capillaries — Efferent fibres to these vessels are in the form of non-medullated filaments accompanying the capillaries. They are derived from the sympathetic chain and are the continuations of the periarterial plexuses. When these are stimulated, constriction will result. Dilatation of capillaries in skeletal muscles is due to metabolites. The sympathetic fibres may also bring about changes in the permeability.

Afferent fibres are medullated. Branches may arise from blood vessels on one hand or receptors like the Pacinian Corpuscles on the other. Axon reflexes seem to be due to this double origin.

Capillary circulation can be viewed directly under the microscope in the frog's mesentery, webs of toes and even the lungs.

VASCULAR RESPONSES OF THE SKIN

Arterioles, upon reaching the bases of the dermal papillae turn, to be parallel to the skin surface and give rise to metarterioles, which in turn give off capillary loops. The collecting venules form a plexus known as the subpapillary venous plexus. The capillary loops can be seen at the base of finger nails with powerful illumination.

The colour of skin depends on the state of filling of the venous plexus of veins and also the presence of oxyhaemoglobin or reduced haemoglobin. Skin temperature depends on the amount of blood flowing through the vessels underneath. Skin may be pale and also hot if superficial vessels are constricted, but flow in deeper vessels is rapid. Radiation of heat to surround-

ing objects takes place from the blood in the cutaneous vessels and this is one of the mechanisms for heat loss from the body, involved in temperature regulation.

The White line — Light stroking of the skin with a blunt point brings forth the appearance of a line of pallor (white line) or blanching in about 15 seconds, which becomes maximally visible in about 30–60 sec. and fades away completely in 3–5 minutes. This white trail in the wake of the instrument is due to the expression of blood from the vessels under the skin, along the line of stroking. This is purely a response of the capillaries and is not dependent on nerves.

The Triple Response: This is composed of three responses produced by stroking in different ways.

1. Red reaction — When a pointed instrument is drawn along a line, more firmly than in the case of the white line (see above) a red line or band appears in about 15 sec. and becomes maximally intense in $\frac{1}{2}$ –1 minute and then disappears in about a few minutes to half an hour. The colour turns blue before disappearing. Dilatation of blood vessels is the cause of the red line. The blue change is due to stagnation and reduction of the haemoglobin in the dilated parts of the vessels. A white halo similar to the white line may be seen on either side of the red line.
2. Spreading flush or flare (red flare) — If the stroking is more firmly done or repeated a number of times, redness spreads on either side of the line of stroking for about 1–10 cms. The temperature of the skin rises. The flare appears in about 15–30 secs. after the red line but fades sooner without turning blue. Arteriolar dilatation, dependent on local nervous mechanisms (axon reflex) is the underlying cause.
3. Wheal formation or local oedema — When the stimulus is very strong (eg. — the lash of a whip) the skin becomes blanched along the line of contact and is raised 1–2 mm above the surroundings. In susceptible animals or human subjects, even mild stroking can produce this, and it is

known as Dermographism. Even letters or words can be written on the skin. The wheal is preceded by the red reaction and completely replaces it. The wheal appears in about 1-3 minutes and becomes prominent in 3-5 minutes (surrounded by a red flare). The margins are clear cut in the beginning but later, they merge more and more with the neighbouring skin and in a few hours the wheal disappears totally. Transudation of fluid, produced by the red reaction, into the neighbouring extracellular spaces gives rise to a localised oedema. Nervous mechanisms are not involved in this.

Sir Thomas Lewis, a British Physician, studied the various cutaneous responses described above. He postulated that a mysterious 'H' substance was responsible for these reactions. Later on, histamine was found to reproduce these responses, on injection under the skin. Other substances in addition to histamine, like 5-Hydroxytryptamine and pain producing vasodilator polypeptids—'Kinins', are also released when cells are injured. So also, bee sting venom and wasp venom, may contain vasodilator substances like acetyl choline and the above mentioned agents and these produce the characteristic symptoms. So, many chemical agents may be involved in these skin reactions, acting either singly or together.

Capillary pulsations may be seen in aortic valvular incompetence or due to arterio-venous aneurysms, because of high arterial pulse pressure which is however not the sole cause, but the condition of arteriolar dilatation which may be a concomitant feature.

Capillary pressure — Direct measurement has yielded values around 30 mms Hg on the arterial side and 12 mms or so at the venous end. Heat, venous congestion and histamine, elevate the pressure. Cold, at first, causes a fall followed by a rise above the original level. In Reynaud's disease, pressure is low. *Arteriovenous shunts* — These exist under the skin as well as in lungs and the heart and also in the terminal portions of digits. They are endowed with smooth muscle coverings. Ordinarily, they are constricted, but open out when the temperature is raised or lowered beyond a certain range. On stimulation of sympathetic

nerve fibres, constriction is caused. Adrenaline has the same effect. Mechanical stimuli, histamine and acetyl choline cause dilatation of these shunts. These play a useful role in temperature regulation — to promote greater heat loss by opening up and also to prevent local cooling of a part of the body.

PLETHYSMOGRAPHY

A plethysmograph is hollow and of cylindrical shape. It is of various sizes depending on the use to which it is put. In the case of an arm plethysmograph, the vessel is long enough to enclose the fore-arm completely upto the elbow. Communication between the outer air and that of the interior is prevented by a rubber diaphragm at the open end of the appliance. It has an aperture in the centre through which the fore-arm is introduced, the edges of the opening gripping the fore-arm to make the interior air-tight. A small side tube enables the plethysmograph to be connected to a volume recorder or a Marey's tambour. Changes in the blood flow to a limb or finger can be recorded by the arrangement described. The action of nervous factors as well as humoral agents can be studied in this way. Plethysmographs used for viscera like the kidney, the intestine and the spleen, are known as Oncometers, which are of various shapes, corresponding to the organs for which they are meant. A spleen oncometer can also be used to record changes in splenic volume brought about by splanchnic nerve stimulation.

The Henderson's cardiometer (see Cardiac Output) is also an oncometer which is used to record changes in ventricular volume during the cardiac cycle.

CEREBRAL CIRCULATION

The brain which is the central organ for nervous control of bodily functions, is extremely sensitive to diminution in the quantity of blood supplied to it. Cerebral ischaemia of even 5 seconds duration causes unconsciousness. If the duration is about 20 seconds, convulsions will occur. Cessation of blood supply lasting several minutes, results in irrevocable damage to the brain, from which recovery is not possible.

Role of carotid sinus : The brain derives its blood supply through the two internal carotid arteries and the basilar artery, all of which form the circle of Willis, from which arteries supplying the different lobes and parts of the brain arise. It is possible to inject a radio-opaque substance and visualise the vascular system of the brain by means of X-rays. The cerebral arterioles have a prominent internal elastic lamina, but the muscle tissue is less well-developed than in other parts of the body. The grey matter is relatively much more vascular than the white matter. The venous drainage is by means of dural venous sinuses.

The cerebral vessels receive vasoconstrictor fibres which arise from the cervical sympathetics. The dilator fibres are conveyed through the superior petrosal nerve. All the same, the role of vasomotor nerves in the regulation of cerebral circulation does not appear to be important as far as experimental evidence goes.

Cerebral blood flow has been estimated by means of Fick's principle based on the amount of nitrous oxide (a foreign gas) absorbed by the brain tissue when the gas is inhaled from a bag. The average value for normal blood flow to the brain is about 50 mls per 100 gms of tissue per minute. This amounts to about 750 mls/min. for the entire brain — $1/5$ th of the total cardiac output.

The role of certain factors concerned in the regulation of cerebral blood flow has been investigated. A rise in the mean arterial pressure can bring about a rise in the cerebral blood flow rate at low values of blood pressure (upto 75 mms of Hg). Further rise in the blood pressure does not bring about a rise in the rate which remains constant even when the pressure exceeds 200 mm of Hg.

The skull forms a rigid container for the brain and hence the intracranial contents have necessarily to be of an unchanging volume. Thus, an increase in the blood flow should be accompanied by a diminution in the volume of the cerebrospinal fluid. This fact was recognised long time back and had been dignified by the term Munro-Kellie doctrine. The intracranial pressure

determines the cerebral vascular resistance to flow. With a rise in the former, the latter also rises. A rise in the arterial pressure brought about by cerebral anoxia which itself is a consequence of raised vascular resistance and a rise in intracranial pressure, while temporarily increasing the cerebral flow, may bring about a rise in the intracranial tension as a direct consequence and hence a rise in the vascular resistance. Thus, the purpose of raising the blood pressure is defeated. In the final assessment, regulation of cerebral blood flow, two sets of factors may be considered —

1. Extrinsic control. 2. Intrinsic control.

1. *Extrinsic mechanisms*: The functionally most important receptors in circulation, in the carotid sinus and the carotid body, are situated in the region of carotid bifurcation in the neck. Because of this strategic location, these receptors can detect pressure and chemical changes in the blood at the point of entrance of the vessels into the cranial cavity. In the standing position, since blood tends to collect in the most dependent parts of the body, namely the lower limbs, the blood pressure transiently shows a fall which stimulates the pressoreceptors and generalised compensatory vasoconstriction with increased heart rate occurs, raising the general blood pressure and cardiac output, so as to drive the requisite amount of blood into the cerebral vessels. As mentioned earlier, the cerebral vessels, however, do not reflect the reflex changes in the systemic circulation. The anoxia that may result from the short lived ischaemia at the beginning, in the standing position, is likely to excite the chemoreceptors which also contributes to the rise in the heart rate and vasoconstriction.

2. *Intrinsic control*: This is also referred to as local auto-regulation. The cerebral vessels are very sensitive to variations in blood CO_2 and O_2 tensions. Experimentally, inhalation of air with 6% CO_2 in it, brings about a rise in the cerebral blood flow. Conversely, a fall in the blood CO_2 tension leads to a reduction of cerebral blood flow. CO_2 seems to have a specific effect on these vessels unrelated to changes in pH or in the bicarbonate content of blood. Variations in the O_2 tension of blood seem to

have less pronounced effects than those of CO_2 tension. When cerebral blood flow diminishes, CO_2 accumulates and causes local vasodilation, thereby permitting more blood to flow even though the fall of systemic blood pressure, which led to the cerebral vasodilatation, persists. On the contrary, rise in the cerebral flow, resulting from a rise in the systemic blood pressure, will bring about washing out of CO_2 from the cerebral tissues. As a consequence its tension falls, the blood vessels going into constriction and reducing the cerebral flow even though systemic pressure continues to be elevated. Corresponding mechanisms operate in respect of variations in O_2 tension and these reinforce those due to variations in CO_2 tension. In general, the cerebral blood vessels seem to undergo changes in their calibre in a manner reciprocal to those of the systemic vessels. Because of the auto-regulation, the cerebral blood flow remains constant over wide fluctuations of carotid systolic pressure between 50 and 200 mm Hg. Cerebral ischaemia is manifested only when systolic pressure falls below 50 mm.

The cerebral blood flow – the total quantity flowing to the brain – seems to undergo very little change over a wide range of activity. Thus, there is no appreciable change from the condition of sleep to that of intense mental activity. It is held that local redistribution of blood occurs whenever any part of the brain is relatively more active than the others. Variations of as much as 50% increase in flow may occur in a particular part of the brain, the total net flow to the entire brain not showing any change at all.

Cerebral circulation is clinically important in that vascular accidents like haemorrhage, thrombosis or embolism are common. Paralysis (hemiplegia), blindness and dementia may follow such episodes. It is pertinent to mention in this connection that the internal capsule is a frequent site for such vascular accidents. One of the lateral striate arteries arising from the middle cerebral artery, because of its propensity to be ruptured, makes possible such accidents. In fact, it has been known as the artery of cerebral haemorrhage.

PULMONARY CIRCULATION

The bronchial arteries which arise from the aorta drain directly

into pulmonary veins. The pulmonary artery (from right ventricle) breaks up into two branches, one for each lung. In the lung, each branch divides immediately into short wide twigs which give off smaller vessels, that break into lung capillaries which in turn connect up with the pulmonary veins draining into the left atrium. The minute vessels of the lung, unlike any other vessels, are surrounded by air in the air sacs. They are highly distensible and their vascular bed can change in volume on account of 1) Variations of the intrathoracic pressure, as by the movements of the lungs in respiration. 2) Changes in minute volume of right ventricle. The total surface area of the lung capillaries which is available for gas exchange (respiration) is about 140 Sq. metres. Left ventricular output has not much influence on the volume of blood held, unless the former is increased several fold.

The pressures in the pulmonary circulation are as follows :

Systolic (right ventricle)	— 22 mms Hg
Diastolic „	— 1 mm Hg
Systolic (pulmonary artery)	— 22 mms Hg 1/6th that of aorta (range 12–30 mms Hg)
Diastolic „	— 8 mms Hg.
Mean pressure „	— 15 mms Hg
Pulse pressure „	— 14 mms Hg
Mean pressure (left atrium)	— 4 mms Hg. (1–8 mms Hg)

The peripheral resistance in the pulmonary circulation is very low and so pulmonary artery pulsations are transmitted to the pulmonary veins. Also, the pulse pressure in the pulmonary artery is about 2/3rd that of the systolic, because very little of blood can be held in the pulmonary circulation in diastole. During inspiration 9% of the blood volume is held in the lungs and during expiration 6%.

Pulmonary Venous Pressure— 3 mms H_2O (inspiration)
+ 4 mms H_2O (expiration)

The tone in the lung arterioles is so low that venous stasis may raise the pressure in the arterioles. Also, any rise in the arterial pressure will seriously interfere with the balance between

the hydrostatic and osmotic pressures. The ability to accommodate extra blood is very great in the pulmonary vascular bed. Exercise does not cause changes in pressure in the lung vessels of normal subjects, but in patients with fibrosis of lungs with consequent non-distensibility, arterial pressure increases the pressure in pulmonary vessels. In muscular exercise, the volume of blood held in the lungs is as much as 20% of the total blood volume. Pulmonary artery pressure falls in inspiration and rises in expiration. This is reflected as respiratory variations in systemic arterial pressures, in tracings of the blood pressure.

Though pulmonary vessels are innervated by the vagus and the sympathetic nerves, yet their role in the regulation of pulmonary arterial blood pressure seems to be minimal, if at all.

ARTERIAL PULSE

The examination of the arterial pulse in the wrist by a physician (radial artery pulse) is a procedure in vogue from ancient time. Arterial pulse has been defined as the wave of expansion and elongation, set up at the root of the aorta by the inrush of blood into it from the left ventricle during its systole and spread throughout the arterial tree to the remotest branch. The clinically important characteristics of the pulse are 1) Rate, 2) Rhythm, 3) Volume, 4) Tension, 5) State of vascular wall. These give considerable information about the cardiovascular system. Normally, the heart rate is the same as the pulse rate, except when some of the heart beats are too weak to set up a pulse wave and there is hence a pulse deficit as in Pulsus Alternans. The regularity of the pulse wave reflects that of the heart beat, except when every heart beat cannot produce a pulse excursion. The volume of the pulse is a measure of the pulse pressure and also the cardiac output and is indicated by the distance through which the palpating fingers are moved outwards by the pulse wave. Tension is the pulse analogue of the systolic pressure. It was thought to be denoted by the degree of pressure to be applied by the fingers on the artery, in order to obliterate the pulse. Since it is easier and much more accurate to determine the arterial pressure by means of the sphygmomanometer,

it is advisable to omit this aspect altogether from the examination of the pulse, as opined by Hunter and Bomford in their classical "Clinical Methods".

When the condition of arteriosclerosis affects the vessel wall, as in old age, it is possible to roll the artery like a whip cord, after abolishing the pulse. Normally, the artery cannot be felt at all.

The pulse wave originating at the commencement of the aorta, travels down very fast along all the arterial branches, large and small, at the rate of 4-5 metres/sec. This does not mean that the blood actually flows at this extremely rapid rate. The

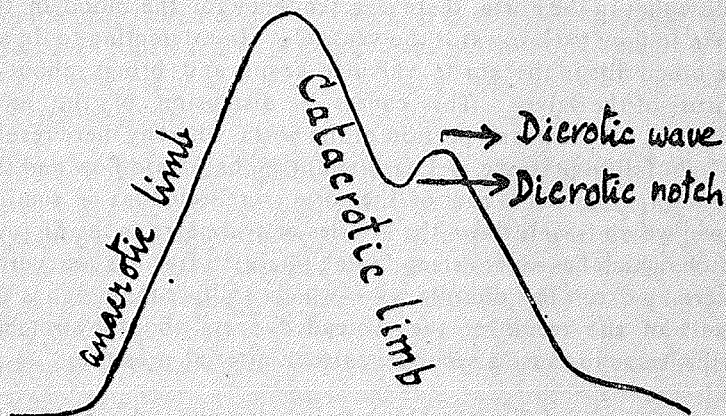


Fig. 18 The Radial Pulse

actual movement of blood occurs much more slowly, at about 20-60 cms/sec. It is the pressure change, however, that travels down at the much higher rate — 10 times faster. The velocity of the pulse wave is dependent on the elasticity of the arterial walls. In stiff and inelastic arteries (old age), the velocity is much higher.

The pulse wave can be recorded by means of a hollow needle placed in an artery and connected to a sensitive pressure recording device. In the students' laboratory, the Dudgeon's sphygmograph enables the recording of the pulse wave in the radial artery at the wrist, on a piece of smoked paper. A tracing thus obtained, shows the following features.

The systolic rush of blood into the arterial tree brings about the rising phase or anacrotic limb. The systole of the ventricle continues even beyond the summit of the pulse wave and ends a little before the occurrence of the dicrotic notch which occurs as follows: There is an acute fall in the intraventricular pressure towards the end of the systole and immediately thereafter, before the diastole actually begins. As the ventricular pressure falls below that in the aorta, there is a tendency for the blood in the aorta to flow back towards the ventricle. In attempting to do so, the blood fills in the aortic valvular cusps and brings about a closure of the valve. This causes a distension of the most proximal (to the heart) portion of the aorta whereby there results a slight fall in pressure. The attempt at backward flow and the fall in pressure at the root of the aorta is reflected as a suction wave, which travels down the arteries and appears as the dicrotic notch, which has a very steep falling phase in tracings of central arterial pulse. The dicrotic wave which follows the notch is the result of the recoil of the distended aorta and the stretched cusps, so as to cause a secondary rise in arterial pressure.

The shape of the central arterial pulse wave is decided by the following factors. Anacrotic limb — The duration of the ventricular discharge influences the steepness of this phase. Shorter the interval, steeper will be the rising phase. Greater the stroke volume, higher and steeper the anacrotic limb will rise. Higher the diastolic pressure, more gradual will be the rising phase (less steep).

Catacrotic limb — With high peripheral resistance, the falling phase will be more gradual. Greater the recoil of the larger arteries, less steep will be the catacrotic limb.

In the peripheral arteries, the shape is further altered by the so-called reflected waves and standing waves, in addition to some

of the factors mentioned already in the case of the central pulse wave, as well as the movement of blood from the arteries into the capillaries. The angularities seen in a central pulse tracing are all smoothened out in a peripheral artery like the radial artery. The carotid pulse differs from the radial pulse in that the former may show small bulges prior to the anacrotic limb, reflecting the rise in intraventricular pressure caused by auricular systole and also isometric contraction of the ventricle. In addition, the incisura (notch) has a very steep down-ward course. There are subsidiary waves or vibrations, both at the height of the anacrotic limb as well as in the catacrotic limb.

The physician can gain valuable information even by mere palpation of the pulse. Conditions like aortic stenosis and aortic incompetence (water hammer pulse) give rise to characteristic pulse waves which can be recognised easily by the clinician.

VENOUS PULSE

The venous pulse (fig. 14) is best seen (if it is seen at all) in the neck region. If one puts a finger on the pulsations of the jugular veins, they are not felt. Because of their very thin walls (unlike arteries), they are liable to be easily compressed. The venous pulse can be recorded by applying a shallow metal cup to the angle between the sterno-mastoid tendon and the inner end of the clavicle and connecting it with a recording (Marey's) tambour. The pulsations that are recorded are due to the transmission of the pressure changes from the right auricle directly to the jugular veins. In other words, jugular pulse tracing reflects the features of the intra-auricular pressure curve. Since the tracing exhibits also other waves than those seen in the auricular pressure curve, it is necessary to simultaneously record the radial pulse tracing for purposes of study of venous pulse. Making allowance for the time interval or delay (1/10 sec.) between the events in the jugular pulse and the corresponding ones in the radial pulse, it is possible to identify the a, c & v as well as the x, x' & y waves of the auricular pressure curve. Much information concerning the cardiac cycle can be obtained by means of the venous pulse tracing which, however, does not yield quantitative data regarding the auricular pressures.

The Mackenzie's polygraph is an instrument by means of which simultaneous recordings of arterial pulse (radial), venous pulse (jugular) and the apex beat, could be had. Its use is somewhat limited, in view of the development of electrocardiography and even in advanced research, intravascular and intracardiac catheterisation and cannulation have made the polygraph obsolete.

VENOUS FLOW

The circulating blood, after having passed through the arterial system and the capillaries, is drained towards the heart through the venous channels. Certain features of the venous flow of blood will now be considered. Several factors as mentioned below, promote the return of venous blood to the heart.

1. The force of the contracting left ventricle driving the blood in its onward course is almost completely spent by the time blood approaches the heart through the great veins. A pressure of about 5 mms H_2O is all that remains of the high systolic pressure of more than 120 mm Hg in the aorta.
2. The volume of blood leaving the arteries — This again is not of significance since the capillary bed is capable of much alteration in size, so as to render insignificant the changes in the inflow from the arterial side. Even the veins can adapt themselves to changes in inflow from the capillaries, minimising their effects. Conventionally, vasomotor control is meant to refer to the alterations in the arteriolar vessels only. The veins are also subject to vasomotor control, though to a less extent.
3. Negative (sub-atmospheric) intrathoracic pressure — This factor has a definite role in promoting venous-emptying into the heart. The veins having thinner walls than arteries, are very susceptible to the respiratory changes in the intrathoracic pressure which is nearly always (except in Valsalva's manoeuvre) negative. There is a suction effect exerted on the blood in veins, aspirating it towards the right atrium — varying from 81 mm H_2O (-6 mm Hg $\times 13.6$) in inspiration, to 34 mm H_2O (2.5 mm Hg $\times 13.6$) in expiration. This

suction effect adds on to the pressure already in the veins, of a few mms H_2O that is derived from the left ventricular action. The thorax thus lifts the blood in the abdominal veins, towards the heart. The deep excursions of the thoracic cage in the greater breathing effort occurring in muscular exercise, enhances the venous return to the heart. When a deep inspiration is made and followed by a forceful expiratory effort with the glottis closed, venous inflow into the heart is impeded. This shows the importance of thoracic movements in promoting the return of blood to the heart. The intrathoracic pressure becomes not only positive but attains a high value (+ 40 mm Hg) and the veins of the face, neck and the limbs become engorged with blood.

4. Action of the right atrium — The stroke volume of the right ventricle is delicately adjusted so as to avoid accumulation of blood in the right atrium and the great veins. It had been denied for a long time that the heart exerted a suction effect on the great veins. If there were any, it was argued that, the veins would collapse on account of their thin walls. Recently, Rushmer has advanced the view that the right ventricle does exert an aspirating action, though to a limited extent, on the auricular blood during its diastole, for which experimental proof has been provided by the work of Brecher. The downward movement of the atrioventricular partition (the A. V. valve is closed) during ventricular systole, causes an increase in the volume of the right atrium which can accommodate more blood.
5. Action of valves and effect of muscular contraction — The presence of valves in veins, especially in those of the leg and arm, promotes one way flow towards the heart. These valves are formed by folds of endothelium. Contracting muscles (abdominal and limb) press on the veins because of the increase in their girth and cause the valves to open and allow flow towards the heart. There is no need for such valves in the veins of the head and neck, since gravity helps the blood flow in the upright or erect position of the body. The importance of the effect of muscular contraction on venous flow to the heart is demonstrated best by the fact that soldiers on parade or sentry duty or policemen directing

traffic, tend to fall in a faint because of diminished venous flow towards the heart. The standing (without movement) at one spot, minimises muscular movements. Human beings are much better adapted to overcome the effects of gravity than animals which do not have well developed mechanisms to prevent syncope (fainting) when held in the vertical position.

The vasoconstriction of splanchnic arterioles, capillaries and veins brings about a reduction in the total vascular bed and hence blood is driven into the larger venous trunks.

Venous Pressures : This can be measured by means of the Von Recklinghausen's apparatus which consists of a cylindrical chamber with a large opening at the bottom and a glass window at the top to enable the veins on which the capsule or chamber is placed, to be seen. Two side tubes are provided, through one of which the chamber is connected to a water manometer and through the other, air can be pumped into the chamber to raise the pressure inside. When the pressure in the chamber is raised sufficiently, the vein is collapsed and this value of the pressure is read in the manometer. One precaution to be observed is that the part of the body in which the vein lies should be at the same level as the right auricle in order that the hydrostatic pressure due to the weight of the blood column, when the levels are different, will not be added to the venous pressure. The pressure in the peripheral veins far away from the heart ranges between 60 and 100 mms H_2O and it falls progressively to just a few millimetres of water, near the right atrium as it is approached through the larger and larger veins. For every 35 mms distance, the pressure falls by 13.5 mms H_2O or 1mm Hg. In the case of the upper part of the body, the pressure in the jugular vein at the lowest part of the neck is around zero — the positive pressure in the vein and the negative pressure exerted from the thoracic cavity balancing each other. Below the heart it is zero, where hepatic vein enters the inferior vena cava. Pressures in the veins should be measured, keeping them at the level of the heart. In the case of the external jugular vein, the zero pressure level shifts from just above the clavicle in the upright position, to the angle of the lower jaw, as the posture approaches recumbency,

though its vertical distance from the manubrium level is kept constant.

It was formerly considered dangerous for the jugular vein to be punctured because it was feared that air would be sucked in from the atmosphere leading on to fatal air embolism. Such a contingency may only bring about a collapse of the vein, preventing air entry. It is also estimated that quite a large volume of air — about 500 cc. will have to enter the vein to really culminate fatally and this large volume can by no means find its way into the vein because of the collapse of the vessel.

Venous pressures rise whenever circulation is obstructed by mechanical means or in congestive failure of the heart. In muscular exercise, a marked rise occurs to the extent of 20-50 mms H_2O , but this disappears very soon at the end of the exercise.

VELOCITY OF BLOOD FLOW IN VESSELS

Mean lineal velocity: An idea of this, in capillary vessels in the frog, can be had by studying the progress of a red blood cell in the capillaries of the web of foot or in the mesentery. The rate of movement is rather slow.

Ludwig's Stromuhr and Reins's thermostromuhr are instruments used to determine the velocity of flow in arteries and veins. These instruments can be used only in experimental animals, since their use requires the insertion of two cannulae into the blood vessel used for the determination. The time required to displace completely, a known volume of oil (immiscible fluid) in the stromuhr, by blood, is found and knowing the diameter of the vessel, the velocity can be calculated. In the case of thermostromuhr, a short length of the blood vessel is enclosed in the heating coil (electric) of the instrument, without in anyway tampering with the continuity or flow in the vessel. The temperature of the blood on either side of the coil is noted and from the amount of heat imparted to the blood by the electric current and the gain in temperature and diameter of the vessel, the flow velocity is computed. No direct measurements have been made in the human subject. Other instruments have also been utilised—bubble stromuhr, differential stromuhr of Fleish.

VELOCITIES IN DOG

Large arteries : 100—200 cm/sec.

Capillaries : less than a millimetre/sec.

Medium and large veins : ranging from very slow upto the rate in arteries.

Lineal velocity decreases as the diameter of the vessel is reduced.

CIRCULATION TIME

Circulation time is the duration taken for a red cell to be transported once through both the systemic and pulmonary systems. In an animal, potassium ferro-cyanide is injected into a peripheral vein and the blood from a punctured vessel is made to fall on a rotating drum covered with a paper soaked in ferric chloride solution. When the prussian blue reaction appears, it signifies the completion of circulation through the pulmonary and systemic circuits. In humans, methylene blue is injected into the vein of one arm and the time taken for discoloration of the opposite arm is noted. Similarly, when sodium chloride solution is injected intravenously on one side, the fall in the electrical resistance of the blood on the opposite side is detected electrically by means of a wheatstone bridge. However, in practice, total circulation time is not always determined. In one method, fluorescein is injected into an arm vein on one side and the appearance of fluorescence on the opposite side or in the mucous membrane of the mouth is looked for, the whole procedure being conducted in darkness. This gives either the arm to arm or arm to mouth circulation time. Similarly, histamine in a small dose can be administered into an arm vein and the time interval elapsing before the appearance of flushing on the face, is noted. A sweet or bitter substance may be given intravenously and the time taken for the perception of the sweet or bitter taste in the mouth is noted. Even radium in a minute dose can be used for determining circulation time. A tiny quantity of radium is introduced into a vein in the cubital fossa of one side and the time taken for the arrival of radio-activity at the right auricle and at an artery in the opposite arm (cubital

fossa), are noted. The interval between the appearance of radio-activity in the right auricle and that in the opposite artery gives the crude pulmonary or lesser circulation time. A more accurate determination is possible by injecting a minute dose of cyanide into an arm vein and noting the exact time when hyperpnoea occurs due to stimulation of the chemoreceptors when cyanide arrives at the carotid body. The following figures represent the values obtained for circulation time —

1. Total circulation time — about 20 seconds in the fluorescent method.
2. Pulmonary circulation time — about 10 seconds, using the cyanide method.

The circulation time normally is constant, at rest. It is reduced during muscular exercise and as an effect of the action of adrenaline. Pathologically, in hyperthyroidism and anaemia, it is reduced. Circulation time is lengthened in myxoedema, high blood pressure and in cardiac failure.

THE BLOOD PRESSURE

The blood pressure (B.P.) as measured by the indirect method using the sphygmomanometer, is the lateral pressure exerted on the walls of the vessels by the contained blood. The systolic arterial pressure is the maximum pressure in the arteries during systole; the diastolic pressure is the lowest pressure during diastole. The pulse pressure is the difference between the diastolic and systolic pressures.

The direct method, entailing the use of a cannula which is introduced into an artery, measures the end-on pressure which is greater than the lateral pressure, as the former includes not only the lateral pressure on the elastic arterial wall but also that derived from the conversion of the kinetic energy of the moving blood column as it meets the resistance at branchings of arteries as well as the increment of pressure caused by the reflected wave therefrom.

Normally, the three readings of blood pressure conform to a definite proportion: systolic: Diastolic: Pulse pressure:: 3:2:1. The mean arterial pressure is the diastolic pressure plus 1/3rd of the pulse pressure. It is the alteration in this that is responsible for bringing about vasomotor or cardiac reflexes into operation. A rise in the mean arterial pressure excites the baroreceptors of the carotid sinus and the aortic arch. A fall inhibits the receptors.

PHYSIOLOGICAL VARIATIONS

a) Age—(the figures refer to systolic BP, in this account). At birth it is 20–60 mm Hg (average–40 mm Hg). It rises to 70 mm Hg by the 15th day and to 80 mm Hg in a month, and to 105 or so at about the 12th year of age. At puberty, a sudden rise to 120 mm Hg is seen in boys (17 years). In girls, an increase occurs upto the 15th year, then a fall upto 18th year and then a gradual rise. BP at 60 years—140/80. The systolic is said to rise by 0.5 mm per year and the diastolic by 0.2 mm per year, though after 20 years of age this is not to be regarded as strictly physiological.

Sex: Women, upto menopause, have BP 5 mm lower than men of the same age, but at menopause an abrupt rise is seen and thereafter it remains above values for men of the same age.

Build: Higher values are seen in broad chested persons. Obese persons are prone to have higher pressures and also are likely to go in for hypertension (high blood pressure).

Race: Western races have higher values than orientals. This is probably due to better build or diet.

- b) Digestion: BP rises during the first hour after a meal.
- c) Sleep: BP falls by 15–30 mm during first few hours of sleep, and then rises gradually and attains the values of waking hours by morning.
- d) Posture: Diastolic is higher while standing than in sitting posture. It is least in recumbent attitude. The carotid sinus mechanism plays a part in these variations.

- e) Emotional influences: Higher values are seen in states of excitement due to central influences and adrenaline liberation. A fall of BP (vasovagal attacks) occurs in susceptible persons due to emotional depression.
- f) Exercise: Systolic is more affected than diastolic especially in moderate exercise. Both central and peripheral factors are at play in this. BP comes down to normal in a few minutes after cessation of activity. First, there is a steep fall due to splanchnic vasodilatation and this is followed by a rise and then a gradual fall.

Certain important Physiological relationships: The product of pulse pressure (PP) and Pulse rate (PR) is an index of the energy of ventricular contraction which is constant under basal conditions. $PP \times PR = 40 \times 72 = 2880$. Increased cardiac output, as in exercise, will alter the value. Also, B. P. is proportional to the product of cardiac output and peripheral resistance.

ESTIMATION AND GRAPHIC RECORDING OF BLOOD PRESSURE

Direct method: Mention must be made of the pioneer work of Rev. Stephen Hales, in 1732. He inserted a brass cannula into the femoral artery of a horse and observed the rise of blood in a long glass tube connected to the cannula by a length of goose's trachea which served as a flexible tube. The blood rose about 8' 3" in the tube. It rose and fell with the systole and diastole of the ventricle.

Also, direct recording of arterial pressures in the central arteries of a dog by means of calibrated hypodermic manometers has been done and this has been tried in man also. This is easier in the femoral and bronchial arteries of man, though the pressure pulses in the peripheral arteries are not quite identical with those in the aorta. However, with the exclusion of air from the apparatus and proper calibration, it is possible to obtain valuable information, especially of the transient changes in the pressure otherwise unobtainable by the indirect clinical method described below.

Cannulating arteries during surgical operations has been tried. At present, large indwelling hypodermic needles connected to optical manometers introduced into accessible arteries are the means of study of human blood pressure. Indirect methods, obviously, yield values lower by 5-10 mm than those obtained by direct methods.

Indirect method: These involve the measurement of pressure necessary to compress a limb — eg. — an arm — and thereby to obliterate the arterial pulse below the region of compression, as of the brachial artery, using a suitable instrument — a U-tube mercury manometer as devised by Riva-Rocci or a modern modification such as the Baumanometer (a mercury cistern replacing one of the limbs of the U-tube). or an aneroid type manometer such as Tyco's.

A flat rubber bag of width at least 12 cms covered by an indistensible envelope of silk or cotton fabric is wrapped snugly (neither too tight nor too loose) around the upper arm, the lower edge of the bag (armlet) being a few centimetres above the cubital fossa. The rubber bag is connected by a length of rubber tubing with a mercury manometer and by a side tube with a pump which is used to inflate the armlet to any desired pressure which can be read off on the manometer. A small valve between the pump and the bag permits the escape of air when it is required to deflate the bag.

Precautions: The subject is seated comfortably on a low stool with his arm resting on a table. The subject should be mentally calm and physically at ease. No single reading by itself is of much significance. When in doubt, readings are taken again, afresh.

Blood pressure readings are first taken by means of the palpatory method and then they are used as a guide for the determination by the more accurate auscultatory procedure. In the former, however, the value for diastolic pressure cannot be obtained.

The radial pulse is felt and the pressure in the armlet or cuff is raised gradually till the pulse disappears. The pressure at

which this happens is noted. The pressure in the bag is raised further and then the valve is opened to lower the pressure. The pulse reappears and the pressure is noted. The average of the two readings will give the systolic pressure. The diastolic pressure however, cannot be determined this way. The readings obtained tend to be lower than those got by the auscultatory method, by about 5 mms, due to the personal factor.

Auscultatory Method: The brachial pulse is looked for in the front aspect of the elbow and the bell of the stethoscope is applied to that area and air is pumped into the cuff. The pressure is raised to a level above the value obtained by the previous method. Then the pressure is gradually reduced. When the pressure falls to the systolic level, certain sounds begin to be heard. These are known as KOROTKOW'S SOUNDS and they are utilised in the estimation of the pressure. KOROTKOW'S SOUNDS may be defined as sounds heard by auscultation of the brachial artery below the cuff when the pressure is lowered from the systolic level to the diastolic level. They are not related to the heart sounds. No sounds are heard normally over the brachial artery when listened to, through a stethoscope, as the flow of blood along the arterial channels is inaudible.

mmHg

- | | | | |
|-----|---|--|--|
| 120 | — | Sudden appearance of clear tapping sound, first faint but growing louder during the next 10 mm Hg fall in pressure | The onset of the sounds give the systolic value. |
| 110 | — | The sound takes on a murmurish quality during the succeeding fall of 15 mms fall in pressure. | |
| 95 | — | Sounds change little in quality but become clearer and louder during the next 15 mm fall in pressure. | |

- 80 — Sounds become muffled in quality and last during next 5-6 mm fall.
- 75 — Final cessation of all sounds. This level gives the diastolic value.

A conventional way of expressing the blood pressure reading is as follows: B. P — 120/80.

When it is desired to repeat the procedure, it is better to completely deflate the bag to zero pressure and reinflate it. In this way, errors arising out of arterial spasm can be avoided.

There was much discussion in the years gone by as to when exactly the diastolic reading is to be taken — whether at the time the sounds get muffled or when they disappear totally. It is not easy to decide when muffling of the sounds actually takes place. The consensus of cardiologists in America is that the disappearance of the sounds occurs at the true diastolic level.

The Physiological significance of the systolic, diastolic and the pulse pressure readings: The systolic pressure represents the total kinetic energy of the blood derived from the ventricular contraction. It is subject to greater variations under normal conditions than the diastolic. It is a less reliable index of the state of the vascular system than the diastolic.

The diastolic pressure on the other hand, has greater significance.

1. It represents the constant load which the vascular walls carry throughout the arterial system.
2. It reflects the state of the peripheral vessels.
3. It determines the filling of the coronary arteries.

The pulse pressure is an index of ventricular output. The pulse pressure is also a measure of the variation of the kinetic energy of the heart.

Regulation of blood pressure: The following are the factors regulating blood pressure :

1. The pumping action of the heart : the rate and the stroke volume.
2. The peripheral resistance: viscosity of blood, lumen of vessels and velocity of flow.
3. The quantity of blood in the arterial system.
4. The elasticity of the arterial walls.

Under normal conditions, only three factors are involved in determining blood pressure: Alterations in the heart rate and systolic discharge and variations in the run-off from the arterial system caused by active changes in the size of the arterioles and perhaps the capillaries.

Changes in rate and output are the central factors and factors influencing the vessels are peripheral factors.

The influence of the various factors mentioned above can be studied by means of mechanical circulation models.

1. A sudden increase in the heart rate, with the venous inflow constant and other factors unaltered, will cause a greater rise in the diastolic than in the systolic, as the outflow from arteries is unaltered but the inflow is increased. The diastole being shortened, less blood leaves the arteries than what comes into them. The pulse pressure is reduced. Increased systolic discharge increases both the systolic and diastolic, but the former more and so the pulse pressure is increased. Decrease in heart rate or in cardiac output will have opposite effects.
2. *Peripheral resistance* is the resultant of the following factors in order . a) active changes in the calibre of minute vessels through vasomotion induced by reflex or humoral agents—this is described separately under vasomotor mechanisms. b) passive alterations in size due to internal or external variations in pressure. c) modification of the viscosity of blood.

Peripheral resistance is the load against which the ventricle pumps blood. It is due mainly to the impedance offered by the minute vessels—the arterioles—As blood flows past the arterioles there is a drop of at least 50–60 mm Hg in the systolic pressure. Only 20 mm fall is seen in the large arteries. The greater part of the peripheral resistance is due to the vessels in skeletal muscles and the splanchnic areas. The peripheral resistance is directly proportional to the mean arterial pressure and inversely proportional to the rate of blood flow.

$$\text{Thus, peripheral resistance} \propto \frac{\text{Mean arterial blood pressure}}{\text{Rate of blood flow}}$$

If the rate of blood flow is increased and the mean arterial pressure is decreased, a reduction in peripheral resistance occurs. With an increase in peripheral resistance, systolic and diastolic pressures are raised, but the latter rises more and so the pulse pressure is decreased.

Velocity of flow: the higher the linear velocity the less is the lateral pressure on the walls of the vessels. But, as the total cross-section increases as blood flows down the arterial tree, the velocity decreases. Cross-section is increased 300–500 times in capillaries. In case of vasoconstriction in arterioles, the linear velocity is much reduced as a result of which the lateral pressure is much increased.

Viscosity: The greater the viscosity the higher is the pressure required to force a fluid along a length of narrow tubing. If blood pressure is constant, then the fluid will take longer to traverse the tube. The internal friction developed within the fluid will be greater if the viscosity is greater. Blood is about five times as viscous as water. Viscosity influences the outflow of blood from the arterial system into the capillaries and veins. The outflow is lessened as the viscosity increases. Increase in viscosity raises the diastolic pressure just like changes in lumen of arterioles. Viscosity is increased in the venous blood due to larger size of RBCs, and also in polycythaemia, hyperglycaemia etc. It is decreased in anaemia, hypoproteinaemia, haemorrhage.

raised body temperature etc. The higher viscosity of blood as compared with water is important in helping to prevent eddies in blood flow.

3. *The quantity of blood in the arterial system:* In any closed system of tubes, the fluid must fill them so that a pressure can be developed within them. As the arterial walls are elastic and distensible, a certain degree of stretching must occur before any appreciable pressure is created. Loss of blood, if not compensated for by other factors, must inevitably cause a fall in pressure. This is remedied by transfusion with blood or a substitute. Loss of blood affects both systolic and diastolic equally.
4. *Elasticity of arterial walls:* This is important in the maintenance of diastolic pressure and also the mean pressure. This does not come into play at low pressures. It is due to this factor that the pulsatile flow in the larger arteries is rendered continuous in the peripheral portions of the vascular system. The elastic recoil of the arterial walls, so to say, acts as a subsidiary pump to drive the blood onwards in a continuous stream between the heart beats. A decrease in elasticity, as in old age, will cause less stretching and so, will lead to an increased systolic pressure. The role of elasticity of larger arteries in providing a subsidiary pumping system is, however, being questioned now.

Decline of pulse pressure and mean arterial pressure in the arterial tree: It is the pulsatile flow in the arterial vessels that is responsible for blood pressure to rise and fall, between the systolic and diastolic levels, with every beat of the heart. But the systolic and diastolic fluctuations become smaller and smaller as blood flows towards the capillaries in which, under normal circumstances, pulsatile flow ceases and is replaced by smooth or nonpulsatile passage of blood. In other words, pulse pressure falls to zero. As blood flows from the larger to the smaller vessels, the mean arterial pressure also declines, initially gradually (about 10 mm Hg) and in the arteriolar vessels very steeply (by about 60 mm Hg). It is this system of small vessels which have a preponderance of plain muscle tissue in their walls that

offer the (peripheral) resistance to the onward flow of blood. Because of the ability of these vessels to alter their size (lumen) over a wide range on account of their innervation, they are of great importance in vasomotor mechanisms regulating arterial blood pressure.

Splanchnic nerve and cardiovascular effects of its stimulation :

The splanchnic nerves are formed by the preganglionic sympathetic fibres arising in the spinal cord (4th to 11th thoracic segments in man) and passing to the collateral ganglia—the coeliac and superior mesenteric ganglia. A few fibres may be derived from the lumbar roots also. Some preganglionic fibres, however, pass on to the viscera where they end on the terminal ganglia situated in the viscera themselves. When the splanchnic nerves are stimulated, the blood pressure shows a rise which is step-like, the first elevation being due to a direct vasoconstrictor effect on the splanchnic vessels, the second accounted for by the release of catechol amines from the adrenal medulla. The liberated adrenaline also causes contraction of the splenic capsule in the dog and thereby diminution in splenic volume which can be recorded by means of a spleen oncometer.

THE REGULATION OF HEART RATE

The normal heart rate in an adult male is about 70 beats per minute. In a woman, it is a little more — by about 5 beats or so. In a new born infant, it is around 130 (100—160). At the end of the first year of life, female babies have a higher heart rate than male babies. After this, till they attain the 8th year of age, their rate happens to be less than that of males. Thereafter the rate in males is less than in females of the same age, till about middle age (50 years). Posture seems to have an influence on heart rate, which is lowest in the recumbent position. It is higher in the sitting posture and highest while standing. During sleep, there is a fall in the rate upto 10 beats per minute. Muscular exercise is the most important physiological condition in which there is a pronounced rise in the rate. States of emotional excitement also bring about a rise in rate. On the contrary, a sudden fall may occur in a state of acute emotional shock and

this may bring on a fainting fit — vasovagal attack. The term tachycardia means a rise in the rate, and bradycardia, a fall.

The minute to minute regulation of the heart rate is under the control of a medullary cardiac centre made up of two components — the cardio-inhibitory and the cardio-accelerator centres. The former has been identified with the dorsal nucleus of the vagus itself. Electrical stimulation of this centre brings about a fall in the rate or even a complete cessation of the heart beat. The exact location of the cardio-accelerator centre is not precisely known. The existence of such a centre is even questioned. It is said to be situated close to the dorsal nucleus. Of the two, the inhibitory centre is the dominant one. To bring about cardio-acceleration, the depression of the cardio-inhibitory centre appears to be necessary. The converse however, is not true.

Cardiac innervation: a) The cardio-accelerator centre is connected with the lateral horn cells in the 3rd and 4th dorsal spinal segments by means of nerve fibres descending in the spinal cord. The pre-ganglionic fibres arise from the cells in the spinal cord and coming out of the cord, they enter the sympathetic chain of ganglia to ascend to the stellate ganglion (inferior cervical and 1st thoracic ganglia usually found fused in man) and middle and superior cervical ganglia. Post-ganglionic fibres arise from these ganglia and travel in the superior, middle and inferior cardiac nerves, to approach the heart, and in association with the vagal fibres, these form the two cardiac plexuses — viz. the superficial and the deep plexuses. The accelerator fibres traverse the plexuses and terminate in the various parts of the heart. It is estimated that the nodal or the junctional tissues receive more fibres than the musculature of the heart itself. Stimulation of the sympathetic fibres to the heart results in raised rate, increased force of contraction, rise in conductivity and excitability of the heart. Coronary vaso-dilatation is another significant effect.

b) The vagus arising from the dorsal nucleus conveys the inhibitory fibres to the heart which are routed through the two cardiac plexuses. The right vagus is believed to give off more fibres to the sino-atrial node than to the rest of the heart. The

left vagus nerve supplies more fibres to the auriculo-ventricular node, than to the other parts of the heart. Stimulation of the right vagus brings about, mainly, a fall in the rate (inhibition). The most marked effect of excitation of the left vagus is a slowing of the conduction in the bundle of His. These effects do not occur in isolation. The other effects of vagal stimulation are also seen when either of the vagus nerves is stimulated. To sum up, the stimulation of vagus brings about, by an effect on the pace-maker, a slowing of the rate or even complete stoppage of the heart, depending on the strength of the stimulus. The auricle has its systole shortened as well as its refractory period. In the case of the conducting system, there is slowing of conduction or even partial or complete heart block with the ventricle beating only once for every 2 or 3 auricular contractions. The ventricle shows reduced force of contraction.

The diminution in the rate and force of contraction of the heart leads to a steep fall in blood pressure and in mammals, this may have a fatal termination.

In the frog, stoppage of the heart on vagal stimulation is temporary. The heart resumes its beat after a short while even though vagal stimulation is continued. This phenomenon is known as vagus escape. The effects of vagal stimulation are mediated by acetylcholine (see Autonomic Nervous System), the parasympathetic neuro-humoral agent. Though vagus escape has not been explained satisfactorily, two tentative hypotheses have been advanced. 1) On continued stimulation of the vagus, the acetylcholine stores of the nerve are exhausted and so the inhibitory effect cannot be sustained.

2) It is believed that the cardiac muscle fibres and the nodal tissue become refractory to the effect of acetylcholine when they are exposed to it beyond a certain duration. Since vagus escape is a common laboratory observation in the pithed frog, Marey's law, Bainbridge reflex and such mechanisms which require the integrity of the nervous system, cannot be invoked to account for it.

The two vagi nerves jointly exercise a restraint on the heart so that the rate of the heart does not rise appreciably under

steady conditions. The cardio-inhibitory centre keeps on sending down the two vagi, a continuous stream of impulses to stabilise the heart rate at a certain level. This influence of the cardiac centre on the heart rate, mediated by the vagus, has long been known as the vagal tone. The afferent drive for the cardiac centre for maintaining the vagal tone is derived from the impulses coursing up the sino-aortic nerves and generated from the carotid sinus, the aortic arch, the carotid and aortic bodies. The existence of vagal tone is best demonstrated by sectioning both the vagi (in experimental animals), this resulting in cardio-acceleration. The effect of double vagotomy can be simulated by the use of atropine which paralyses the vagal terminations (pharmacological vagotomy) or by the de-afferentation of the sino-aortic region on both sides. Vagal tone is minimal in a new born infant and consequently the cardiac rate is high. Vagal tone is pronounced in athletes and those accustomed to heavy physical activity. Their cardiac rate is less than those with sedentary habits.

Certain terms were used by earlier authors to describe the different effects of vagal stimulation on the heart. These are: chronotropic effect — a fall in the rate; Dromotropic effect — depressed conduction; Bathmotropic effect — reduced excitability; Inotropic effect — diminished contractility.

The heart rate is subject to variation depending on the factors operating. Changes in the heart rate appropriate to the different physiological conditions, are brought about *mainly* by alterations in the vagal tone. The role of the sympathetic fibres seems to be a subsidiary one. The cardiac centre is itself subordinate to various nervous as well as chemical influences. Impulses descending down from certain areas in the cerebral cortex, like area 13, can modify the heart rate. Emotional effects are mediated by this mechanism. The excitation of the anterior and the middle group of hypothalamic nuclei causes a fall in the rate, while a rise in the rate can be elicited from the posterior nuclei.

Rhythmical variations in the rate are observed in the two phases of respiration — a rise in inspiration and a fall in expira-

tion. These changes are sought to be explained as being due to anyone or all of the following possibilities — 1) afferent impulses from the lungs to the cardiac centre. 2) variations in pressure on the right side of the heart acting reflexly. 3) irradiation of impulses from the respiratory centre to the cardiac centre.

Sino-aortic mechanisms:— The stimulation of the baroreceptors, as by a rise in the mean arterial pressure, reflexly brings down the heart rate. A fall in blood pressure results in a rise in the rate. Thus heart rate is inversely proportional to blood pressure and this relationship is referred to as Marey's law.

Chemo-receptor reflexes: Changes in the tensions of oxygen and carbon dioxide in blood bring about reflex effects. Anoxia accelerates the heart as does moderate excess of carbon dioxide (hypercapnia). The rise in heart rate (tachycardia) is due to the activation of the chemo-receptors of the carotid and the aortic bodies. By a direct effect on the cardiac centre, these changes bring about a slowing of the rate (bradycardia). Acapnia (fall in carbon dioxide tension), by a direct action on the centre, brings about an acceleration of the heart. In asphyxia, initially, reflex slowing of the heart occurs due to rise in blood pressure. But, as the heart weakens, blood pressure falls and the rate rises. In mild asphyxia, a delayed inhibition of the heart may be seen after recovery occurs, due to after-discharge from the cardio-inhibitory centre. Breathing oxygen-rich air causes reflex bradycardia. A rise in H-ion concentration also, by chemo-receptor activation, evokes a rise in the heart rate.

Engorgement of the great veins and the right chambers of the heart as occurs when venous inflow increases, brings about a rise in the rate. This effect is attributed to the Bainbridge reflex (auricular reflex). The afferent and efferent fibres for this effect are present in the vagus itself. Though some authors doubt the existence of Bainbridge reflex, yet the evidence against it is not very conclusive.

Impulses generated in certain parts of the body under abnormal conditions bring about a slowing of the heart — for eg. — a blow on the abdomen (in violation of the rules of boxing)

will cause a cardiac arrest. Occasionally, when the ear is syringed, the heart may stop on account of the excitation of Arnold's nerve (the auricular branch of the vagus). These are rather bizarre effects and have no place in the normal regulation of the heart.

A rise in the body temperature, as in states of fever, causes cardio-acceleration. The impulse generation rate of the pacemaker is greater due to its metabolic activity being raised. At 100°F the pulse rate is 100 per minute. For every degree (Fahrenheit) of rise above this, the pulse rate has been observed to rise by 10. In certain fevers, however, the heart rate is less than what one would expect from the temperature.

Though a rise in intra-cranial tension is not a physiological factor, yet in view of its association with a lowered heart rate, it merits mention in this connection.

Certain hormonal factors effect changes in the heart rate as follows: Adrenaline which in the isolated heart of all species causes acceleration of the heart, yet acting on the intact heart slows it because the rise in blood pressure (as a result of adrenaline action) is an earlier effect and this in its turn causes reflex slowing of the heart. If atropine is administered prior to adrenaline, cardio-acceleration will occur concomitantly with rise in blood pressure. Atropine abolishes the sino-aortic reflexes by paralysing vagal terminations. Thyroxine is responsible for tachycardia. The mechanism of its action is one of raising the impulse generation rate of the sino-atrial node. In hyperthyroidism, there is a sustained elevation of the heart rate and in myxoedema, the heart rate is less than in normal subjects. These alterations are permanent unless the underlying thyroid condition is treated, when the heart rate becomes normal. Other factors like vasopressin (when administered in therapeutic doses and not secreted in minute physiological doses) and renin (acting through angiotension) bring about a fall in rate which is the reflex sequel to the pressor effect of these factors. Theoretically, imbalance between calcium and potassium ions in blood can lead to changes in the heart rate.

In the foregoing account, the possible role of all usual and unusual factors has been discussed. It needs to be emphasized that the presso-receptor mechanisms operating in the sino-aortic region provide the minute to minute control. Chemical factors do not ordinarily exert their effects unless there are metabolic upsets, as in muscular exercise. Thus, higher neural control originating in the cerebral cortex and the hypothalamus is important in bringing about anticipatory changes, especially in preparation for muscular exertion. The fast heart rate that goes with states of excitement points to the importance of higher nervous control over the cardiac centre.

PRESSORECEPTORS AND CHEMORECEPTORS

It has been observed by many workers that, at several points in the vascular tree and even in the chambers of the heart, there are pressure sensitive areas. In addition, in a few situations, there are specialised structures composed of 'glomus cells' which are specially susceptible to chemical changes in blood. These structures are somewhat away from the main circulation and are built around certain branches arising from the major arteries like the aorta and the carotid artery. The influence of chemical factors in respiration was suspected even in the last century, and subsequently, several workers like Dale and Evans added on to the knowledge regarding chemical control of respiration. The importance of the Carotid Sinus in regulation of heart rate and blood pressure was shown by Hering in the early part of this century. A few years later, Heymans established firmly the role of the carotid sinus, the aortic arch and the carotid and aortic bodies, in the control of circulation and respiration.

The carotid sinus is the localised dilatation of either the common carotid trunk just below its bifurcation or more commonly of the commencement of the internal carotid artery. Nerve endings are seen to ramify in the walls of the sinus and disposed mostly in the tunica adventitia and to a less extent in the tunica media. A rise in the mean arterial pressure causes a stretching of the walls of the sinus, thereby exciting the nerve endings which consequently have come to be known as presso-receptors or baroreceptors (sensitive to pressure changes like a

barometer). Similar receptors have been revealed in the walls of the aortic arch. These nerve endings are always in a state of basal excitation and the impulses generated in them are conveyed to the medullary centres — Cardio-inhibitory and vasomotor — along the nerve of Hering, a branch of the glossopharyngeal nerve in the case of the carotid sinus, and vagal fibres which join the vagal trunk on either side, in the case of the aortic arch. In the rabbit, there is a separate nerve trunk arising from the aortic arch and joining the vagus and named the aortic depressor nerve. Even at basal levels of the mean arterial pressure (and hence systolic and diastolic pressures), the sinus nerve and the vagus show a steady discharge of impulses ascending them. If the mean pressure is increased, discharge frequency increases and thereby brings about a rise in vagal tone and a fall in the heart rate (by acting on the cardiac centre) and fall in blood pressure—vasodilation (acting on the vasomotor centre). In the event of a fall in mean arterial pressure, opposite effects occur. It has been found that the baroreceptors are most sensitive at basal levels of the mean arterial pressure. More about the role of these receptors in circulatory adjustments has been discussed in relevant sections on the heart rate and the vasomotor regulation. It has been shown that certain vasoactive agents like adrenaline, by a direct action on the walls of the carotid sinus and aortic arch, can cause effects like a rise in the blood pressure itself.

In between the two branches of the common carotid artery—the internal and external carotid arteries—is seen a small structure, a few millimetres in size, the carotid body which is found to enclose a branch of the occipital artery which itself arises from the external carotid artery near its commencement. The glomus caroticum or the carotid body is composed of glomus cells or chromaffin cells (having affinity for chromic acid and staining brown with it) and these are bathed in blood which passes through the substance of the carotid body which is one of the most vascular, weight for weight, of all the organs in the body. The carotid body is innervated by the nerve of Cyon which joins the 9th cranial nerve. A similar structure, known as the aortic body, has been identified in close relation to the arch of the aorta. The sensory innervation of the aortic body

is by fibres which join the vagal trunk. Both these bodies are concerned mainly with the reflex chemical regulation of respiration, but with circulatory adjustments also, to some extent. These functions are based on the sensitivity of the cells (chemoreceptors) of the carotid and aortic bodies to certain changes in the chemical composition of the arterial blood — fall in oxygen tension, rise in carbondioxide tension and a rise in H-ion concentration. Changes in the opposite direction with regard to the two respiratory gases and the H-ion, depress the cells. These structures send a constant barrage of impulses to the respiratory, cardiac and vasomotor centres. The frequency of discharge fluctuates, depending on the level of activation of the chemoreceptors. It is the opinion of certain workers that the chemoreceptor reflexes are not very important *under physiological conditions* even for respiratory regulation.

Work on the carotid body has shown that agents like the cyanide radicle, lobeline, nicotine and acetyl choline, when injected into the blood stream, can act directly on the chemoreceptors to produce respiratory changes tending to increase pulmonary ventilation.

It is worthwhile pointing out that while widespread vascular effects are obtained from stimulation of the baroreceptors in the carotid sinus, the most significant consequence is that the blood flow to the brain is maintained constant under various circumstances. Thus, the aptness of the location of the sinus baroreceptors in the neck — in a vessel (carotid artery) which is a major arterial channel for the circulation to the brain, is revealed. The sinus, as it were, stands as a guard to the cerebral circulation at the very commencement of the blood flow to the brain. Thus, the carotid sinus and the aortic nerves well merit the name 'buffer nerves'.

CROSS CIRCULATION TECHNIQUE

This method of establishing the exchange of blood between two or more experimental animals, was introduced late in the last century by Fredericq. The purposes for which it was developed were: 1) to study purely humoral effects, of an experimental

procedure in an animal. 2) to observe purely nervous effects in an animal without complication by humoral effects.

The usual method is to connect an isolated vascular bed of the test animal with the cardiovascular system of another animal, the heart of which (donor) provides the energy for blood flow in the isolated vascular bed of the recipient animal. Heymans made use of this technique in demonstrating the effects of stimulation of the carotid sinus baroreceptors or chemoreceptors, as well as the stimulation of splanchnic nerves. Cross circulation was established not only between two dogs but in some experiments, in three dogs. In one type of cross circulation experiment, Heymans united the carotid artery of the donor animal (dog) with the carotid artery of a second animal (dog) below the carotid sinus region in the latter and the latter's artery was 'anastomosed' with the jugular vein of the first animal. Thus, blood pumped from the heart of the donor flowed to the carotid sinus (only) in the recipient and returned to the donor's circulation. The suprarenal vein of the second animal was linked with the jugular vein of a third animal in which an oncometer was placed round the spleen. By this set up it was shown that when there was a fall in the arterial pressure in the first dog, a pressor response (rise in blood pressure) occurred in the second dog on account of sympathetic discharge in the latter. The catechol amines released (as a result of sympathetic action) in the second animal were made to circulate in the third animal in which splenic contraction was brought about and this was recorded by a spleen oncometer. The baroreceptor reflex in the second animal produced by a fall in the blood pressure in the first animal, released hormones whose action was demonstrated in the third animal.

VASOMOTOR MECHANISMS

A reference has already been made to these under the discussion on 'Regulation of blood pressure'. Active changes in the calibre of the smaller blood vessels which are brought about by reflex nervous mechanisms or humoral agents constitute an important mode of blood pressure regulation.

The existence of vasomotor nerves was first demonstrated by the classical experiment of Claude Bernard who on cutting the cervical sympathetic in a rabbit, observed dilatation of arterial vessels in the ear of the rabbit. The nervous mechanisms involved in the control of blood vessels, arteries, arterioles, veins and venules are co-ordinated by a medullary vasomotor centre which sends nervous impulses to the plain muscle cells of the blood vessels through nerves known as vasomotor nerves. By this means, either vasoconstriction (narrowing of the lumen) or vasodilatation (widening of the blood vessels) is caused. Of the different parts of the vascular tree, it is the arterioles which have more of plain muscle tissue in them than any other vessels. All the same, the part played by the veins and venules is considerable in view of their holding 65-70% of the total blood volume, while arteries accommodate 15%, the heart 5-10% and the capillaries another 5-10%. While usually a discussion of vasomotor regulation is taken to refer to control of arterioles and arteries, especially as a part of maintenance of blood pressure, it has to be stressed that the mechanisms which are going to be described are not only concerned with the arterial side of the circulation, but also the venous channels. The effects arising from the operation of the many vasomotor mechanisms are, however, better seen in the arterial vessels.

The existence of a medullary vasomotor centre was revealed in animal experiments as follows: A section of the spinal cord just below the medulla, caused an acute fall of blood pressure. After a few hours, the blood pressure rose to almost the previous level owing to the taking over of the control by a subsidiary spinal centre. If now the spinal cord was destroyed, the blood pressure fell to a low level once again. After a few days, there was an attempt at restoring the blood pressure to nearly the original level. This effect was taken to be the result of an inherent or automatic tone developed by the blood vessels themselves in the absence of a central nervous control.

The vasomotor centre consists of a diffuse network of interconnected neurones in the reticular formation, extending from the lower pons to the obex (inferior angle of the IV ventricle). Electrical stimulation of certain areas in this region brought on vasoconstriction (rise in blood pressure) or a pressor effect. The

vasoconstrictor centre is said to occupy the apex of the ala cinerea or the fovea inferior. The depressor effect or fall in blood pressure (vaso-dilatation) was elicited from an area lateral to the obex on either side. Thus, the centres are present on both sides of the mid line and the halves are intimately interconnected. The vasoconstrictor and vasodilator areas are reciprocally connected. Of the two, it appears that the vasoconstrictor area is dominant over the other. For vasoconstriction to occur, a depression of the dilator centre is not necessary, whereas for vasodilation, the vasoconstrictor centre has to be inhibited with or without activation of the vasodilator centre.

It is the opinion of some workers that vasodilation can be brought about without the mediation of the medullary centre, as occurs in the anticipatory phase of muscular exercise, during which dilatation of skeletal and coronary vessels occurs on account of impulses coming down from the cerebral cortex by-passing the vasomotor centre. It is also held that vasoconstriction in the other parts of the circulation may occur as a result of impulses originating in the cortex and descending down pathways without the intervention of the vasoconstrictor centre. Yet another view is that vasodilatation is not due to nervous mechanisms at all, but is locally induced by humoral agents which can cause dilatation of blood vessels in the face of a constrictor influence originating in the vasomotor centre.

Vasomotor nerves: The medullary vasomotor centre is connected with those cranial nerve nuclei whose outflow convey vasodilator fibres, the spinal vasoconstrictor centre and the sacral vasodilator fibres through pathways descending in the spinal cord.

Vasoconstrictor nerves: Langley, by means of nicotisation of ganglia, showed the distribution and course of these fibres. The cells of origin of these fibres are present in the intermediolateral column of all the thoracic and the upper two or three lumbar segments. The preganglionic fibres from these cells leave the cord through the anterior spinal roots and the white rami and enter the sympathetic chain of ganglia of the same side. These fibres, either synapse immediately in the nearest ganglion,

or ascend or descend to terminate in a ganglion farther away. Postganglionic fibres, either form peri-arterial nerve plexuses as in the case of the carotid arteries, or enter grey rami to rejoin spinal nerves to be conveyed to their ultimate destinations.

The fibres to the head (and to all structures inside the cranium) originate in the upper two thoracic spinal segments. Their postganglionic course is through the peri-arterial plexus around the carotid artery on either side.

The upper limb derives its constrictor fibres from the 4th to the 10th thoracic segments, the peripheral course being along the brachial plexus. The viscera of the abdomen and the pelvis receive fibres arising in the lower thoracic and the upper lumbar spinal segments. The preganglionic fibres form the major and the minor splanchnic nerves. Splanchnic vasoconstriction is a major circulatory adjustment very necessary for raising the systemic blood pressure as well as for re-distribution of blood to the active skeletal and cardiac muscles in muscular exercise. Experimental stimulation of the splanchnic nerve not only brings about vasoconstriction of the abdominal and pelvic vessels, but also the release of catechol amines from the adrenal medulla which is innervated by preganglionic fibres arising in the spinal segments and passing through the sympathetic chain without interruption. (See Autonomic Nervous System). The rise in blood pressure that occurs as a marked effect of splanchnic nerve stimulation, is partly due to the release of adrenaline and nor-adrenaline in addition to splanchnic vasoconstriction.

Vasoconstrictor fibres for the lower limb arise in the lumbar segments and these eventually reach the peripheral vessels by being routed along somatic nerves of the limb.

The thoracic and abdominal walls receive their constrictor nerve fibres through the appropriate spinal nerves.

The fibres for the heart travel in the vagus itself.

Vasodilator Nerves: Vasodilator nerves do not form a definite anatomical entity like the vasoconstrictor nerves. Vaso-

dilator fibres may not take part in reflex regulation of blood pressure. They may be only concerned with local vasodilatation to supply blood to active tissues. Their central origins are probably directly connected to efferent fibres without intervention of the vasomotor centre. They consist of: a) parasympathetic b) sympathetic c) antidromic fibres.

The vasodilator nerves do not exert a tonic action like the constrictors.

Parasympathetic vasodilator fibres: The distribution of vasodilator fibres from the cranio-sacral outflow is well known, but whether vagus gives vasodilator fibres to the thoracic and abdominal viscera is doubted. Vasodilator effects in glands may be due to metabolites, though some vasodilator fibres as such also may exist. Parasympathetic vasodilator fibres are cholinergic, though resistant to atropine. All autonomic fibres seem to have a low impulse discharge rate.

Sympathetic vasodilator fibres: These seem to be present only in skeletal muscles and perhaps also in coronaries and certain proximal skin areas. The fibres are cholinergic and affect blood flow to muscles by a discharge rate similar to constrictor fibres. They are centrally connected to an area very near to the motor cortex. Bilateral connections from anterior part of hypothalamus and midbrain passing lateral to and probably not connecting with vasomotor centre, have been thought to exist. Their significance is unknown and they are not concerned with blood pressure regulation. Perhaps they are excited in alarm reactions resulting in flight or fight which require redistribution of blood to muscles from viscera. They also perhaps take part in increasing blood flow to muscles before exercise starts. Even fainting may be due to their central excitation. That there is a motor unit type of distribution in peripheral vessels, is strongly favoured by some authors. The dilator responses may be even due to inhibition of constrictor tone but an active dilatation may also be superposed. The latter, however, can be blocked by atropine.

Antidromic vasodilator fibres: In animal experiments, it was seen by Stricker and later by Bayliss, that excitation by any

form of stimulus, of the distal portion of a sectioned dorsal spinal root of the lumbosacral region, produced vasodilatation in the hind limb. Stimulation of the central end of an afferent nerve, even after the sympathetic chains of ganglia had been destroyed, brought about vasodilatation especially in cutaneous blood vessels. All this indicated that the dorsal roots of the cord convey vasodilator fibres which are apparently sensory fibres normally conveying impulses towards the spinal cord, from the periphery. This was questioned later and plausible alternative explanations have been put forward in support of the view that these fibres are really efferent and not afferent. All the same, it is not possible to refute the existence of 'afferent' fibres which, in a manner contradictory to their usual physiological role act as depressor or vasodilator fibres conveying impulses to the blood vessels away from the cord.

Factors influencing the vasomotor centres :

- 1) Nervous
- 2) Chemical or hormonal.

1) Nervous factors: These are of three categories—

- a) somatic influences
- b) visceral reflexes
- c) vascular reflexes

Somatic influences :— Stimulation of central end of somatic sensory nerves causes rise or fall in blood pressure depending on the strength of stimulation. Pain sensation brings about similar effects — rise or fall in blood pressure depending on the severity of pain. Cold causes vasoconstriction and heat, dilatation in skin vessels. Opposite effects are seen in the visceral vessels.

Visceral influences :— Stimulation of afferent nerves of the viscera, as by compression of testes, pulling on the mesentery, distension in intestines, will have effects depending on the intensity of stimulation.

Irradiation of impulses from the respiratory centres causes changes in the blood pressure during inspiration and expiration.

Vascular reflexes :— These are of importance in regulating the tone of the vessels and hence blood pressure, from minute to minute. Pressoreceptors in the walls of carotid sinus (afferents from the ninth nerve) and aortic arch (afferents through vagus) are stimulated by increase in blood pressure and bring about reflex vasodilatation (depressor reflex). Fall of blood pressure gives rise to opposite effects (pressor reflex). (Pacinian corpuscles act as pressoreceptors in the mesenteric vessels).

Drugs which, when applied directly, cause constriction or relaxation in the carotid sinus, will reflexly bring about fall or rise in blood pressure, respectively. Sinus wall contains stretch receptors in series and in parallel with the muscle fibres. The former are excited by distension and active constriction of the vessel but the latter are excited by only distension.

Loven's reflex :— Reflex vasodilatation in an active organ is accompanied by constriction elsewhere, thereby bringing about re-distribution of blood to the active organ.

Axon reflex :— An impulse travels up one branch of an axon and down another branch and brings about vasodilatation. This is not a true reflex as no nerve cell is involved in this. Axon reflexes are initiated by painful stimuli and involve the cutaneous fibres responsive to thermal stimuli. Axon reflexes may be mediated by adrenaline or acetyl choline. Pain fibre axon reflexes help in local protection of tissue, as in frost bite and signal danger by pain sensations. Also, an axon reflex helps in local repair and defence by increasing blood flow.

Chemical factors influencing the vasomotor centre :— Carbon dioxide is the most important of these. Increase in carbon dioxide content of blood causes vasoconstriction by a direct action on the centre. The blood pressure rises. The effects are enhanced by vagal section, as this puts out of action the cardio-inhibitory reflexes controlling increase in blood pressure.

Asphyxial hypertension is of the same mechanism. Lactic acid acts similarly. Decrease in CO_2 content of blood causes vasodilatation. Chemical changes in blood also act reflexly through the carotid body and aortic body mechanisms.

The carotid sinus mechanism was demonstrated conclusively by cross circulation experiments of Heymans.

Chemical agents that act directly on the arterial musculature:— Vasomotor nerves liberate humoral substances at their terminations which act on the walls of the vessels. Also, products of tissue metabolism act similarly—directly on the vascular musculature. Vasodilatation is brought about by carbon dioxide and lactic acid acting directly.

Hormones:— Adrenaline causes constriction of all vessels, except coronary vessels and muscular branches. Vasopressin, on the other hand, causes vasoconstriction everywhere.

Role of renin and hypertensin is discussed elsewhere.

Histamine causes vasodilatation by a direct action on the vessels.

In tissues like brain and heart, metabolic needs determine the patency of vessels. Peripheral factors are more important, as it will be dangerous for these organs to depend on a remote vasomotor centre.

Many vessels are partly controlled by vasomotor nerves and partly by metabolites. Usually, peripheral vasodilators (metabolites) are more powerful than vasoconstrictor nervous influences, so that the tissue always gets enough blood supply. Thus ischemia is avoided. According to recent ideas, the cortically induced vasodilatation is of prime importance (and not the action of vasodilator substances) in increasing the blood supply to active muscles during exercise.

CARDIAC OUTPUT

Definitions:

Stroke Volume (SV) is the amount of blood pumped out by a ventricle in a single beat. Axiomatically, in steady states, each

ventricle expels the same volume of blood as the other. In the human adult, SV at rest is about 70 cc.

Cardiac Output or minute volume is the quantity of blood ejected by a single ventricle in a minute. By definition, $C.O. = S.V. \times \text{heart rate}$. In the human adult, C. O. at rest, is between 4000 and 5000 cc.

Cardiac Index (C. I.). C. O. is found to be proportional to the body surface area. C. O. expressed in terms of the body surface is called Cardiac Index. It has a value of about 3 litres per sq. meter of body surface. C. I. is more in athletes and in people accustomed to heavy muscular work.

Physiological variations:

1. Age: In children, C. I. is more, as BMR is greater; in women C. I. is less than in man.
2. Training for physical work: Individuals with greater muscular development resulting from physical training, show higher C. I.
3. Temperature: C. I. rises above resting value at environmental temperatures exceeding 30°C.
4. During digestion of food, C. O. rises by about 30–40% of its resting value, an hour after the intake of food. The rise is maintained for about 3 hours and then C. O. gradually declines to original value.
5. Gross variations in the composition of inspired air cause alterations in C. O.
6. A little reduction in C. O. may occur during sleep.
7. Posture: In recumbent attitude of the body, C. O. is more than in standing posture. The heart rate varies in the opposite direction.

8. **Muscular exercise:** C. O. is increased to a degree, depending on the severity of the exercise. The maximum values attained range between 20 and 35 litres in very severe exercise, the limit being dependent on the build and training of the subject.
9. **Emotional states:** Increased output occurs in states of fear or anxiety.
10. **Pregnancy:** In the later months of pregnancy, a rise in C.O. is seen on account of the increased blood volume.

Methods of determining Cardiac Output

a) *Cardiometer method in experimental animals:* In an animal like the dog or cat, the chest is opened and artificial respiration is instituted. The pericardial sac is slit and the Henderson's cardiometer is slipped over to enclose the ventricles completely, the edge of the hole in the rubber diaphragm gripping the heart along the auriculo-ventricular groove. The inside of the cardiometer is air tight and communicates through its outlet with a piston recorder. Changes of volume of air inside the cardiometer, occurring as a consequence of the changes in the volume of the ventricles (caused by their systole and diastole), can be recorded graphically. By appropriate calibration, the excursions of the piston recorder on the smoked drum could be made to give volume changes in the ventricles, directly. The difference between the volume during diastole and the volume in systole gives the stroke volume of both ventricles, half of which will be the stroke volume of one ventricle. The C. O. or the minute volume can be got from the product of S. V. and the heart rate. This method was used by Starling and his colleagues in the heart-lung preparation to record C. O. graphically. This is an experimental procedure and as such, not suited for clinical application. Also, the values for C. O. obtained are less than for intact hearts, obtained by other methods.

b) *Application of Fick's principle:* Though this principle was formulated for estimating C. O. this could be extended to measure the blood flow in any organ. The object in applying this principle is to find out the output of the right ventricle which over any reasonable period, is the same as that of the left ventricle.

As blood passes through the lungs, it absorbs oxygen and gives out carbon dioxide in a definite proportion. How much gas exchange occurs depends on the rate of blood flow through lungs. One could measure the arterio-venous difference in content of either oxygen or carbon dioxide. At the same time, the oxygen consumption per minute or the carbon dioxide output rate from the lungs could be measured. From the formula given below, the right ventricular output (and hence that of the left ventricle) can be derived.

$$\text{C. O.} = \frac{V}{a - v} \times 100 \text{ where } V = \text{volume of oxygen absorbed in a minute (in the lungs) or of CO}_2 \text{ evolved in a minute (in lungs).}$$

a = arterial content of oxygen or CO_2 per 100 cc of blood.

v = venous content of oxygen or of CO_2 per 100cc of blood.

The oxygen absorption rate or the CO_2 output per minute, in the lungs can be found by means of the Douglas bag or with the use of a spirometer (see the account on respiration).

To find out the arterial and venous contents of oxygen and CO_2 , two methods have been used.

1. **The Indirect Method:** This is the earlier of the two methods. For various reasons, CO_2 rather than O_2 is the gas dealt with in this method. The CO_2 content in arterial and venous blood is arrived at indirectly. A sample of alveolar air (at rest) is analysed for its CO_2 tension which is the same as in arterial blood. From the tension of CO_2 in arterial blood and by reference to the CO_2 dissociation curve for arterial blood, its content of CO_2 (in volumes per cent) can be obtained. The CO_2 output rate is determined by the technique already referred to.

As for estimating the tension of CO_2 in mixed venous blood (leaving right ventricle), a cumbersome procedure is followed, the details of which are variously described by different authors. In essence, the CO_2 content of mixed venous blood can be determined by finding the composition of a gas mixture in the lungs which neither gives up nor acquires CO_2 . Such a gas mixture has CO_2 under the same tension as blood in pulmonary capillaries (mixed venous blood). From a CO_2 dissociation curve for venous blood (physiological dissociation curve), the actual content of CO_2 can be got. This procedure is, as mentioned above, rather difficult to carry out and a number of errors creep in.

Procedural details: The subject takes three deep breaths from a gas bag having 5 litres of a mixture of 94% oxygen and 6% carbon dioxide, the high content of oxygen being meant to avoid ill effects of anoxia. The three breaths should not occupy more than 15 seconds (less than the systemic circulation time at rest, of about 30 secs), because no time should be allowed for blood which has taken up CO_2 in lungs, to come back to the lungs, so as to establish an equilibrium between alveolar air and the continually renewed venous blood in the pulmonary capillaries. The third breath is held for a few seconds and a sample of alveolar air is collected and its CO_2 tension is found. From the assumption that the alveolar air is now in equilibrium with the venous blood in the lungs, it follows that the tension of CO_2 in the former is the same as in the latter. By reference to the dissociation curve for CO_2 , the content of CO_2 in mixed venous blood is obtained.

The Direct Method of Applying Fick's Principle :

The technique of Barcroft for animals and that of Cournand for humans, have led to the possibility of a direct sampling of mixed venous blood from the right atrium (or right ventricle or even pulmonary artery). A very slender flexible catheter can be passed into the ante-cubital vein (under aseptic precautions) and pushed in under fluoroscopic control till the tip is seen to enter the right side of the heart. The catheter can be left in situ and serial samples, if required, of mixed venous blood can be collected for analysis. Arterial blood samples can be had by a direct puncture of an easily accessible artery like the femoral.

Values for C. O., resulting from the direct method, are taken as standard and are higher than those obtained by methods such as using foreign gases (to be mentioned below). In skilled hands, this method is practically without risk.

2. Application of Fick's principle using inhalation of foreign gases like acetylene, nitrous oxide or ethyl iodide, has been in vogue for some time. Acetylene seems to be the choice on account of its innocuous nature, but such determinations yield values for C. O. which are much lower than those obtained by the direct method (1).

Stewart's Principle: A suitable dye, Evan's blue or any other is used for this purpose. It should satisfy the same criteria as for estimation of blood volume. A small quantity of blood is withdrawn from a vein. A definite amount of the dye to be used is added to a measured amount of the sample of blood in order to prepare a standard solution. A known quantity of the dye (W) is injected into a vein and at intervals, arterial blood samples are taken and analysed for their content of the dye. The concentra-

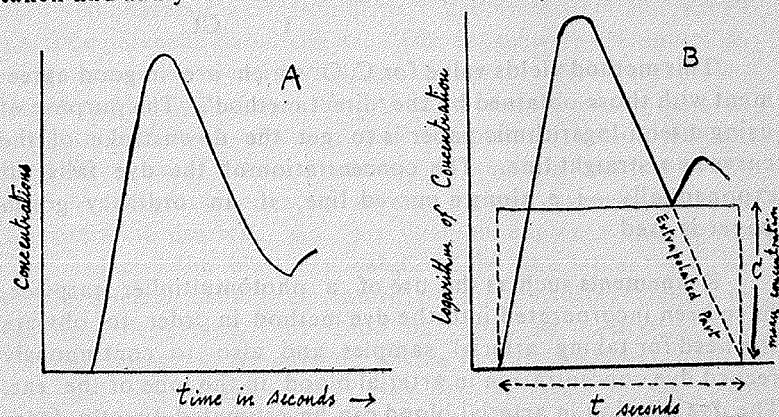


Fig. 19. When an ordinary graph paper is used as in (A) The downstroke of the curve representing the fall in concentration of the dye in the samples is along a curve which cannot be extrapolated to meet the X-axis in order to derive the mean concentration of the dye. If however the logarithms of the concentrations of the samples are represented along the X-axis (as in B) the downstroke of the curve will be a straight line which can be extended to meet the X-axis.

tion of the dye is plotted against time on a semi-logarithmic graph paper. The upstroke of the curve thus obtained is straight. After reaching a peak it dips down, but a second hump appears a little later due to recirculation of the dye. But the downstroke from the first peak which is straight is extended to meet the X-axis. The interval of time (t) from the first appearance of the dye in a sample, to the point of intersection of the extrapolated curve with the X-axis is noted. From the triangular area bounded by the curve, the mean concentration of the dye (C) during the above mentioned interval of time, is derived. It follows that the quantity of dye injected, completely passed through the heart in t seconds in a volume of blood (V) with concentration (C) of the dye. (Fig. 19).

$$W = VC \text{ and } V = \frac{W}{C}$$

V is the volume of blood pumped in time t .

$$\text{So the cardiac output C. O.} = \frac{V}{t} = \frac{W}{Ct}$$

This method yields value for C. O. which are in good agreement with those obtained by the 'direct method'. The purpose of using a semi-logarithmic paper is to get the downstroke of the curve as a straight line. The concentration of the dye falls off exponentially —i. e. along a curved line, if an ordinary graph paper is used.

Refinements such as the use of a photomultiplier earpiece, have been incorporated into the dye method in order to obviate the need for taking arterial samples and also to continuously record dye concentration in arterial blood in the lobe of the ear. The dye dilution in arterial blood can be estimated directly from the skin colour which is the parameter or quantity measured by the above-mentioned special device.

Radio isotopes like ^{131}I have been used in the same way as the dye mentioned above. Arterial puncture is thereby rendered unnecessary, the concentration of the isotope in the blood in the aorta is recorded continuously by means of a scintillation detector (focussed over the blood vessel) activating a recorder.

Other methods : one method of indirectly arriving at the cardiac output is to study the size of the heart shadow in two planes during the phases of the cardiac cycle by means of serial X-ray photography.

Yet another method is ballistocardiography which is somewhat empirical.

The pulse pressure recorded from an artery is also made use of to estimate the cardiac output, it being regarded as a measure of the stroke volume.

KNOWLTON-STARLING'S HEART-LUNG PREPARATION

The Heart-Lung preparation, though not originated by Knowlton & Starling, was made practicable by them. It was utilised to study the behaviour of the isolated heart as a pump, under different conditions — i. e. — when each of the several factors like blood pressure, heart rate, venous return etc. was altered independently of others. Necessarily, the heart had to be denervated completely (section of vagi and sympathetics), so as to exclude nerve mediated effects. The lungs were left intact in order to aerate the blood perfusing the heart. Peripheral resistance offered by small arteries and their branches was simulated by an artificial device— 'a thin-walled rubber tube enclosed in a rigid glass or metal tube, alterations in the air pressure in the latter changing the capacity of the former, even completely collapsing it if desired. An 'air cushion' enclosed in a glass bottle replaced the elasticity exhibited by the larger arteries like the aorta. The temperature of the perfusing fluid was maintained constant, but could be varied as desired. The hydrostatic pressure at various points in this artificial circulation could be measured by cannulae suitably placed and attached to mercury manometers with recording floats. C.O. was measured by means of a cardiometer communicating with a piston recorder or a tambour.

In addition to other things, the effect on the C. O. of independent variation of arterial blood pressure (by raising the pressure in the device for peripheral resistance) or the venous pressure, or the heart rate (by stimulating the distal end of the cut vagus with varying strengths of stimuli) was studied. The findings were as follows :

1. When the 'arterial' pressure was raised suddenly, the stroke volume fell, the ventricle failing to empty itself. The residual blood was added to the freshly arrived venous inflow and this resulted in increased diastolic volume which now caused more forcible contraction. The output rose and the original stroke volume was reattained. The energy output of the heart was however, greater as a result of work against a higher load.
2. A larger venous return by stretching the ventricles to a greater extent evoked an augmented stroke volume and this led Starling to enunciate his famous law of the heart that 'the energy of contraction, however measured, is a function of the length of the muscle fibre'.
3. When venous inflow and arterial resistance were kept constant, altering the heart rate did not affect the cardiac output unless the heart rate was very high, when output was reduced.

FACTORS CONTROLLING CARDIAC OUTPUT

It follows from the definition of C. O. that it depends on two parameters or variables — viz — heart rate and stroke volume. Variations in heart rate or stroke volume or both can be logically expected to result in altered cardiac output.

Heart rate: This is under the control of the cardiac centres in the medulla which (the centres) are themselves subjected to many influences, both chemical and nervous. The heart rate is adjusted according to needs. An account of the regulation of heart rate is found elsewhere.

The ventricles get filled during diastole, the major portion of blood arriving in during the initial part of diastole — rapid filling phase. Much less quantity of blood flows into the ventricle in the slow filling phase or diastasis. The contribution by auricular systole is variable and negligible, at rest. When the heart rate is faster, the systole is shortened but the diastolic phase is more curtailed, especially the diastasis. However, if the rate is not sufficiently high—less than 100 beats per minute, the length of

diastole is not much affected. Though individual beats of the heart may be slightly less productive with unchanged venous flow, the minute volume will be more than that with the heart rate at rest. Heart rates over 100 per minute will entail a greater reduction in stroke volume, with the result that the C. O. may not be much more than the resting value. At very high rates of the heart beat (without concomitant changes in other factors), the diastasis is abolished and inroads are made into the rapid filling phase. Hence, the stroke volume will be very much diminished and the minute volume may actually be less than the normal value (at rest). However, in exercise, increased rate helps to raise C. O. because venous return is also increased. Cardiac output rises with heart rate upto about 200/minute.

Stroke Volume : For more than two decades after Starling's classical experiments with the Heart-Lung preparation, it was taken for granted by most workers that increased venous return (during muscular exercise) was the only causative factor in the increase of stroke volume. Rushmer and others cast doubt on the applicability of Starling's Law with regard to the causation of increased stroke volume. In experiments involving roentgenographic studies of the cardiac shadows in humans as well as in animals in which inductance gauges and other devices in situ were also employed, it was seen that the end diastolic volume was not larger (in exercise) than at rest. In fact, the findings were that the end diastolic volume and the end systolic volume were smaller than at rest. The ventricle increased its stroke volume by contracting more vigorously and expelling part of the residual volume in addition to the normal stroke volume. This observation proved that the ventricle or for that matter all the chambers of the heart, did not normally (at rest) empty themselves completely. The increased force of contraction has been now attributed to greater sympathetic activity during exercise which increases the contractility of the heart. This is not the whole story. In other studies on humans, it was found that the type of response to exercise varied according to the training of the individual. Even in the severest form of exercise, a sedentary subject increased his output (to 25 litres) by a rise in the rate upto 180/min. and a rise not much more than 50% in the stroke volume. Athletes could attain a cardiac output as high as 35

litres/min. In these, the stroke volume exhibited a greater rise than in the untrained people, though maximum heart rate was still 180/min. The increase in stroke volume resulted from an increase in the force of contraction and not from larger end-diastolic volume. In moderate exercise, a rise in rate was the sole cause of increased C. O. in all classes of subjects. From Rushmer's studies on intact dogs, in whose hearts there were built-in inductance gauges which signalled changes in the ventricular diameter or some similar linear dimension, the following observations were made.

1. The heart rate rose almost instantaneously to a high figure even before the commencement of exercise and this was maintained throughout the exercise.
2. The stroke volume was increased, with a progressive reduction in the diastolic and end systolic diameters of the ventricle. Though the latter remained smaller throughout, the former soon regained the resting value.

The above two mechanisms were considered to be the result of greater sympathetic drive occurring even before the onset of exercise and maintained during activity.

Greater C. O. must, as a consequence, imply a greater venous inflow to the heart. What comes out must get back. Recent work shows that sympathetic activity can also promote venous return in addition to increasing the contractility of the heart. One way is to raise the rate of ventricular filling by making the pressure gradient between auricles and ventricles more steep, as follows: The release of interfascicular tension in diastole (between the layers of cardiac muscle fibres causes a suction effect, normally thought to exist) which is promoted by sympathetic activity during exercise. Secondly, the degree of ventricular filling is also greater during exercise, because sympathetic activity and release of catecholamines into blood, lower the ventricular resistance to filling. Thirdly, the active auricular contribution to ventricular filling is increased due to sympathetic discharge.

Some authors are of the opinion that Starling's law also has a contributory role in raising the stroke volume, in addition to the effect of increased sympathetic activity referred to above. Others believe that the importance of Starling's law in muscular exercise is only in accurately balancing the stroke volumes of the right and left ventricles — i. e. to provide the heart with sufficient blood to pump out and maintain cardiac output.

In summary, changes in C. O. are brought about by increased discharge of impulses from the cerebral cortex and hypothalamus, even before the onset of muscular exertion. Increase in C. O. is mainly brought about by an increased heart rate, supplemented in severe exercise by a rise in the stroke volume (caused by greater contractility of the heart) which is also the result of increased sympathetic discharge. Increased venous return which follows increased C. O. only helps to provide more blood to be pumped out by the heart, but by itself does not augment stroke volume. Promotion of venous return to heart seems to be also due to greater suction effect by the ventricle, less resistance to stretch and greater auricular output, all three of which result from the sympathetic hyperactivity.

Energy of ventricular contraction and work of the heart :

The heart muscle (mainly or solely that of the ventricles) performs work of two kinds—

- a) in driving blood through the systemic circulation against frictional resistance offered by the vessels in the case of the left ventricle and in overcoming resistance in the pulmonary circulation as regards the right ventricle. This type of work is referred to as static work.
- b) The ventricle also imparts velocity to the blood (ejected from it) as it leaves the ventricle. The total mechanical work of the ventricles is given by the following formula—

$$W = \underset{\substack{\text{(static} \\ \text{work)}}}{7/6 QR} + \underset{\substack{\text{(dynamic} \\ \text{work)}}}{mV^2/g}$$

- Where W = work in kilogram metres per hour.
 Q = Quantity of blood in kilograms, ejected per hour.
 R = the mean arterial pressure in metres of blood.
 m = weight of blood ejected in an hour, in kilograms.
 V = mean velocity of blood at the root of the aorta, in metres per second.
 g = acceleration due to gravity, in metres per second²

While the heart is at rest, static work accounts for almost the entire work output, dynamic fraction being negligible. But when the heart is beating forcibly, the two fractions rise tremendously, the dynamic component becoming almost equal to the static part.

Nutrition of the heart and the fuel for contraction :

The actual blood flow to the heart has been described under coronary circulation. The heart muscle cannot function for long without oxygen being supplied. It can incur very little oxygen debt—about 1/5th that for skeletal muscle. The maximum deficit that is permissible in the case of heart muscle was thought to be 0.06 gm of oxygen per gm of muscle. (for skeletal muscle—0.30 gm of oxygen per 1 gm of tissue). Recent work has indicated that the cardiac muscle can stand more severe oxygen lack than this. The cardiac muscle shows remarkable adaptability in the choice of the fuel for supplying energy for its contraction. A number of substrates could be utilised for this purpose, in contrast to skeletal muscle. Normally, the heart can 'burn' fuels of carbohydrate origin, like lactic acid and glucose. But, if necessity arises, as in fasting states, amino acids, ketone bodies and fatty acids, can be oxidised to furnish energy. Work capacity and performance do not seem to be affected by this.

CARDIAC RESERVE

The heart being the central organ of circulation, provides blood supply to the various organs in particular and the body in general, in sufficient amounts. The ability of the heart to increase

its output to the maximum extent is indicated quantitatively by the upper limit of the cardiac output which is achieved by raising the heart rate and the stroke volume to the greatest heights possible. Even so, the availability of oxygen to the tissues is also determined by the oxygen content of arterial blood and the tension gradient as regards oxygen, between blood and the tissues and also the reaction of blood. Thus, the reserve capacity of the heart to meet extraordinary oxygen requirements of the tissues by raising its output to the greatest degree possible, is utilised most efficiently only when there is also oxygen availability and actual increase in the oxygen utilisation rate of the tissues. In clinical terminology, cardiac reserve means the maximal increase of cardiac output that is possible for a patient's heart. In disease states, especially of the heart itself, obviously, the heart is not capable of meeting severe demands on its output. But from the physiological point of view, cardiac reserve can be expressed in terms of many parameters (factors). A mere rise in the output of heart by itself is of no avail, if the active tissues cannot abstract oxygen from the blood in adequate amounts and sufficiently rapidly. Thus, the enhanced supply of blood can be put to optimum use only if blood can part with its oxygen to a greater extent than normally. The accompanying table gives quantitatively the normal cardiac reserve in its various aspects in the adult male accustomed to severe physical exertion.

	Normal (at rest)	Maximum possible	Reserve
Heart rate	70/min.	200-210/min.	130-140/min.
Stroke volume	60-70 cc.	150-170 cc.	80-100 cc.
Minute volume	5-6 litres	35 litres	30 litres.
Oxygen extracted from 100 cc of blood	4-5 vols.	14-16 vols.	10 vols.
Oxygen utilisation rate.	200-300 cc.	3000 cc.	2700 cc.

It has to be mentioned that the work efficiency of the heart as a pump increases since, even though cardiac output rises and the coronary flow also rises, yet these do not keep pace with the

cardiac work which is increased in severe exercise, to a proportion, greater than what is warranted by the increased blood flow. (See Coronary Circulation).

It has been seen from the work of several authors that stroke volume does not rise, except in very severe forms of exercise, whereas the rise in ventricular output is mainly achieved by a rise in heart rate only, which, however, levels off in severe exercise. Athletes, even at rest, have greater output because of larger sized chambers. Their 'resting heart rate' is lower than in people with sedentary habits. (See Muscular Exercise). Cardiac reserve, it is needless to say, is reduced in disease conditions, especially those affecting the heart muscle itself and also in respiratory disorders.

MUSCULAR EXERCISE

Muscular exercise (work) calls for a coordinated response from the various systems of the body, especially the cardiovascular and respiratory systems which are required to put forth their best in order to meet the demands for oxygen by the active muscles, and also to eliminate the waste products like carbon dioxide and fixed acids such as lactic acid. The magnitude of changes in the cardiovascular and other systems depends on the severity of the exercise which is conveniently graded according to the rise in the oxygen utilisation rate. The oxygen consumption rate in an adult, at rest, ranges from 200 to 250 cc per minute. Exercise, necessitating a rise of oxygen consumption by less than 3 times is termed as light exercise. Moderate to heavy exercise will involve an increase by 3-9 times and severe or maximal exercise implies a rise beyond 9 times the basal rate.

Cardiovascular system : Certain anticipatory changes occur even before the onset of exercise, due to a discharge of impulses from the higher cerebral centres and hypothalamus to the medullary cardiac and vasomotor centres. As a result, the heart accelerates and beats more powerfully, thereby raising the cardiac output or the circulation rate, which means that the tissues which are going to be active are enabled to have an augmented blood supply and consequently more oxygen, at the very outset.

Changes in the vascular bed also occur owing to increased sympathetic discharge and release of catechol amines (adrenaline, noradrenaline etc.) More blood vessels open out in the active muscles and the heart (coronary circulation) and vasoconstriction occurs in the inactive regions like the skin and viscera (Loven's reflex). The rise in cardiac output raises the blood pressure, even though the peripheral resistance is lowered. A higher systolic blood pressure helps the active tissues to get an increased blood supply.

Once muscular exertion commences, more factors come into operation and maintain or even add on to the changes brought about in the anticipatory phase. The fall in oxygen tension (anoxia) and the rise in CO_2 tension in blood (hypercapnia) and a fall in pH (all occur only during exercise) will stimulate the reflex mechanisms through the chemoreceptors of the carotid and aortic bodies, to raise cardiac output further. An increased venous return results from a greater systolic discharge, greater fluctuations of the intrathoracic pressure, the vigorous and larger movements of the diaphragm and the milking action of the active muscles. This augmented venous return, according to the older views, invokes Starling's Law and increases the force of ventricular systole by distending the cardiac chamber. The Bainbridge reflex also may come into operation, consequent on distension of the right side of the heart by greater venous return.

In maximal exercise, the cardiac output can be as high as 25 to 35 litres, depending on the previous training of the individual, the heart rate being trebled and the stroke volume more than doubled.

Recent work has led to the modification of older conclusions arising from the classical experiments of Starling and others. The opinion now is that the increase in heart rate occurs even before the onset of exercise (nerve mediated) and there is no further increase in the rate after the commencement of muscular activity. The greater volume of blood ejected by the ventricle is also due to anticipatory changes brought about by sympathetic drive. Distension of chambers by greater venous return is not held to be responsible for the greater stroke volume. While the

greater output in an untrained person may be the result of the rise in the rate alone, in trained subjects (athletes), greater stroke volume (by about 50-60% above the basal value) partially contributes to the augmented output, but even in these, the rise in the rate contributes a greater share to the rise in the output. In short, all changes aiming at raising the cardiac output are due to the barrage of impulses from the higher centres and occur in the preparatory phase. The onset of muscular work does not make any difference. (For further details refer to discussion on Cardiac output).

One significant fact is that a rise in heart rate occurs concomitantly with a rise in blood pressure: Marey's law seems to be held in abeyance during the period of exercise. The coronary blood flow is increased by as much as 4-5 times, in heavy exercise. Lymph flow is very much augmented in the body.

Respiratory System: As mentioned before, greater oxygen supply to the active tissues and faster removal of carbon dioxide are the objectives towards which adjustments in the respiratory system are directed. A rise in the rate and depth of respiration occurs in varying degrees depending on the size of the muscular effort. Several mechanisms are brought into operation in increasing the pulmonary ventilation. As in the case of the circulatory system, an efferent discharge from the higher centres seems to play a role in increasing the sensitivity of the medullary respiratory centre to the various factors coming into play in the course of exercise. Impulses arising from active muscles and joints are thought to stimulate the respiratory centre to greater activity. The rise of carbon dioxide tension in blood (also acting directly on the respiratory centre), the fall in oxygen tension and fall in pH of blood stimulate the chemoreceptors to effect an increase in the pulmonary ventilation. Rise in body temperature also contributes to the hyperventilation, by a direct action on respiratory centre (heat polypnoea). In moderate exercise, the respiratory rate may be double the resting rate and the tidal volume is increased to 2 litres, giving a ventilation rate of 60 litres per minute. In severe exercise, the rate may be as high as 60/min. and the tidal volume more than 2 litres, the ventilation per minute rising above 100 litres.

The duration over which a sustained effort is possible, depends on the severity of the exercise as well as the previous training of the individual. Light exercise, like walking, can be maintained for a long time. In moderate or heavy exercise, like a long distance race (5000 metres), the initial part is somewhat difficult because metabolites like CO_2 and fixed acids accumulate at a faster rate than can be disposed of through the lungs and by other means. The subject becomes dyspnoeic. This is so because the respiratory and circulatory adjustments have not progressed to a sufficient degree. But, after this preliminary phase of discomfort, the subject suddenly feels relieved of his distress and is now enabled to continue the exercise for a long period. This feeling of comfort in spite of the continuance of effort, is called in common parlance as 'second wind'. In severe exercise like a 'hundred yards dash', the physiological adjustments can never be rapid enough to meet the enormous need for oxygen and to remove carbon dioxide sufficiently rapidly and this form of exertion can be indulged in only for a short while which is less than even a minute. Energy for this degree of effort is derived from anaerobic breakdown of glycogen. There is a limit to the availability of energy from this source which dries up when the products of breakdown accumulate and 'clog' the mechanism (acidaemia is the cause) — no further glycolysis is possible.

Oxygen debt: In the beginning of moderate exercise (before second wind), and throughout severe or maximal exercise, the rate of utilisation of oxygen by tissues is much higher than the rate of oxygenation of blood in the lungs. The body, so to say, functions in the absence of oxygen, meeting its needs by furnishing energy through anaerobic mechanisms (see above). The waste products accumulated need proportionate amounts of oxygen to deal with them through the usual metabolic pathways. The body can be said to go into a "state of oxygen debt", because the body can only supply oxygen 'at its own pace'. The rapidly accumulating metabolites are got rid of subsequent to the actual period of exercise during which they were produced. Oxygen debt hastily incurred is paid off only leisurely. The magnitude of oxygen debt will depend on the severity of exercise which also limits the duration of exercise. The more acute the oxygen debt, less will be the duration of the effort. While skeletal muscles

can put up with oxygen lack (debt); the heart muscle cannot function in the absence of oxygen even for a very short time.

The efficiency of the heart muscle is said to increase in exercise. That is to say that for the same oxygen consumption, more physical work can be turned out. The duration of sustained effort possible for an individual depends on the maximum oxygen debt he can 'tolerate'. Recent work indicates that even the heart can put up with a little oxygen debt.

Respiratory Quotient (R. Q.): The resting R. Q. on a mixed diet, is around 0.8. In light exercise, R. Q. may not change appreciably. In moderate or heavy exercise, before the onset of 'second wind', the R. Q. rises above 1, but later it may come down (though still above 1). In severe exercise, R. Q. may rise steeply to 1.5 or 2 and be maintained there for the duration of exercise. The maximum is attained after the end of exertion. A higher R. Q. than at rest, implies that oxygen is not supplied at a rate fast enough to deal with metabolites and also that fixed acids are being produced at a rapid rate, the alkali reserve being depleted to neutralise the acids. In the immediate post-exercise period, R. Q. goes down below the resting value and remains low for such a time as is required to rebuild the alkali reserve to the original (resting) level. After this, R. Q. returns to the resting value.

Coefficient of Oxygen Utilisation : This rises during exercise from the resting value of about 0.2, the blood leaving the tissues de-oxygenated to an extent depending on the degree of the activity. In maximal exercise, venous blood may contain very little oxygen. In other words, it is almost fully desaturated as regards oxygen.

Increase in coefficient of oxygen utilisation is effected in several ways.

1. The oxygen tension gradient becomes steeper, since tissues use up oxygen at a rapid rate and so the tension of oxygen in the tissue spaces is much less.

2. The rise in temperature displaces the dissociation curve for oxygen, to the right. That is, blood will now hold less oxygen at the same tension, than at normal temperature. More oxygen will be given off to the tissues.
3. The rise in H-ion concentration (due to lactic acid accumulation) when it occurs, has the same effect as a rise in temperature.
4. Rise in CO₂ tension in the tissues has also a similar effect (Bohr effect).
5. Greater blood flow is provided by vasodilatation and also opening up of many capillaries as well as by raised flow pressure (B. P.).

Dead space volume : Physiological dead space is increased during muscular exercise. It forms about a third of whatever the tidal volume is.

Changes in the composition of blood : The magnitude of changes in blood chemistry depends on the intensity and duration of the exercise. Reduction in circulating volume of plasma without affecting the total red cell volume of blood, rise in the RBC count and plasma protein concentration are some of the features seen, during exercise. The loss of water from blood is due to several factors like increased rate of sweating, greater capillary permeability, higher osmotic pressure in the tissue spaces owing to accumulation of metabolites and a rise in blood pressure resulting from greater cardiac output. Arterial blood tension of oxygen in lungs is lower than normally. A reduction by as much as 16 mm. may occur.

Only in maximal exercise, a rise in blood glucose level is seen and this is attributed to accelerated glycogenolysis caused by release of adrenaline. Leucocytosis has been observed in muscular exercise.

Lactic acid is present in blood normally, to the extent of about 15 mgm %. The level may rise upto 200 mgm % accord-

ing to the severity of exercise. In light exercise of short duration, lactic acid may not find its way into blood, but is confined to tissue spaces. In moderate or maximal exercise, lactic acid diffuses out into blood, being produced in relatively large amounts. This is neutralised by the alkali reserve, if adequate and thereby carbon dioxide is liberated and expelled through the lungs. (The RQ rises) Excess amounts are also excreted by the kidney. Further, excess lactic acid causes a rise in H-ion concentration which acts as a stimulus to the chemoreceptors and brings about changes in circulation and respiration. Except in light exercise, oxygen consumption rate seems to be proportional to the rate of lactic acid production. Obviously, the blood bicarbonate (alkali reserve) and blood lactate vary inversely with each other.

In light to moderate exercise, there is no actual acidemia but only acidosis. In maximal exercise, acidemia (i. e.—a change in pH of blood) occurs and this is a potent factor which limits the duration and vigour of the effort.

Changes in renal function: In moderate exercise, an initial rise in urine output may occur consequent on greater vigour of circulation, but in violent exercise (with sweating), renal blood flow is diminished and hence glomerular filtration rate and urinary output will fall. Urea clearance and excretion of chlorides will be reduced while the content of fixed acids like lactic and pyruvic acids, ammonia (to save base, Na), phosphate and uric acid in urine will be more. Albuminuria and even haematuria are seen after very strenuous exertion—a game of Rugby. More creatinine is excreted in the active period, but retention occurs in the recovery phase.

Rise in body temperature: Of the total amount of energy liberated during exercise, only 25% is converted to useful work. The rest is wasted as heat which raises the body temperature by 1°C or more. This heat is lost by means of 1) evaporation of water in expired air. 2) evaporation of water from the skin—perspiration. 3) convection currents caused by movements of limbs and body.

Body temperature rises on account of exercise even in very cold environments — aortic regions. Raised body temperature, as mentioned previously, contributes to effect changes in circulation and respiration.

Fatigue : After steady and prolonged exercise (of moderate degree) or a short bout of very heavy exercise, the subject feels fatigued. Causes of fatigue are not well understood. Chemical and nervous factors seem to contribute to this. Accumulation of lactic acid in muscles is said to be responsible for aching of the muscles. In athletes this is minimal.

Permanent effects of exercise : When a subject repeatedly performs the same piece of work or same exercise, certain beneficial effects accrue. His capacity for exertion is increased as a result of the following changes :

- 1) Increased muscular strength due to hypertrophy of muscle. The cross section of the exercised muscle is larger since the individual fibres enlarge. Muscle fibres not used ordinarily, become larger in size on account of their being used. Part of the increase in size is due to the increase in the number of capillaries which develop. The sarcolemma thickens and the non-contractile tissue increases in quantity. The glycogen stores are greater and myoglobin content is doubled or trebled. The muscle becomes more efficient in dealing with waste products arising out of activity.
- 2) Greater resistance seen as ability to sustain an effort longer, this resulting from a hypertrophied heart (larger stroke volume), increased vital capacity (greater pulmonary ventilation possible) and a rise in alkali reserve. Trained subjects have a lower resting pulse rate due to greater vagal tone.
- 3) Accuracy and sureness of movement are the attributes of a veteran as compared with a novice, in any form of activity: This is the result of improved muscular coordination.

SHOCK

Shock is a rather vague term denoting peripheral circulatory failure, usually seen after severe injury resulting in blood loss

(hence called traumatic shock or even surgical shock) or even in non-haemorrhagic conditions like myocardial ischemia or pulmonary embolism. This entity has also been known as secondary shock, to distinguish it from primary or neurogenic shock coming on immediately after an injury. This latter condition is what is commonly called as a faint reaction—a vasovagal attack—and is excluded from further discussion in this account.

Secondary shock comes on a few hours after injury. The clinical features of shock can be conveniently grouped as under. The patient is apathetic and insensitive to external stimuli. There is a marked fall in blood pressure and rapid, thready (low volume) pulse. The systolic falls to as low as 60 mm Hg and the blood volume is diminished. Even though the heart beats vigorously, the output is poor, bringing down the blood pressure. The cutaneous and splanchnic vessels narrow down, the skin becoming blanched (pale), cold and clammy. Cyanosis of the tips of fingers and toes, is seen. The fall in blood pressure reduces renal flow and urine output falls. Even anuria may occur. Non-protein nitrogen rises with fall in alkali reserve. Haemoconcentration is seen often, though it need not always be present.

The essential cause of shock seems to be a diminution in the circulating blood volume produced by a frank loss of blood as such or the exudation of plasma from blood vessels, as in extensive burns or even loss of protein-free fluid from blood, as in acute salt depletion (cholera), acting either singly or even together. In the beginning stages, there is an attempt to lessen the vascular bed by vasoconstriction, so that the smaller blood volume fills it and also for the maintenance of the cerebral, cardiac and pulmonary circulation. The symptoms of shock supervene when the compensatory mechanisms (see chapter on Haemorrhage) fail. To the effects of diminished blood volume as such, are added, those of loss of plasma or even loss of water, if present. Haemoconcentration, by increasing the viscosity further, slows down flow in capillaries, intensifying the effects of diminished volume. In other words, the features of shock directly result from the gross disparity between the blood volume (very much lowered) and the vascular bed which is relatively much more. It was formerly held that much plasma was trapped in capillaries at sites

of injury, consequently reducing the blood volume and that this was the cause of shock. This impression arose from haemotocrit studies of blood in injured tissues. These are now discredited. The amount of blood lost as such, at the site of injury is usually sufficiently great to produce shock by itself.

On the other hand, dilatation of all capillaries seems to be a major causative factor in shock. While, normally, about $\frac{1}{4}$ th of the blood volume is held in the minute vessels, in states of shock nearly $\frac{2}{3}$ ds stagnates in the capillaries. Some believe that the formation of masses of cells closely adhering together, seen after injury, may be responsible for the slowing of the blood flow and leading on to shock. Blood also collects in great quantities in the outlying parts of the circulation far away from the heart. Thus, capillary dilatation, even in the absence of haemorrhage and reduction in blood volume, can bring about shock. Normally, there is a fine adjustment between the vascular bed and the circulating blood volume. If either the former increases or the latter decreases, blood pressure will fall. If both change in the manner indicated for each, the effect on blood pressure will be pronounced and venous return will be hindered and hence cardiac output will fall. In what is known as Cardiogenic shock, the venous return is not reduced because there is no pooling of blood in the periphery of circulation. In most cases, a diminution in blood volume seems to be a major cause (hypovolemic shock).

Though a few mechanisms — exhaustion of the vasomotor centre, acapnia (fall in CO_2 content of blood), fat emboli resulting from injured bone and subcutaneous tissues, and lastly lack of adrenal cortical hormones — have been thought of in the past as underlying causes of shock, yet their role in bringing about shock has been disproved.

The absorption of toxic materials like histamine (toxaemic-theory) from injured parts of the body, has been held to be responsible for peripheral vasodilatation and hence shock. Isolation of an injured part by means of a tourniquet was observed to delay the onset of shock. When the tourniquet was removed and free circulation to the damaged part was restored, shock-like symptoms appeared. Again, some workers have not noted such results

from the same type of work. Antibiotics have been used with benefit in treating shock. This fact supports the toxæmic theory.

Recently, it was shown that it was the escape of blood and plasma from the vessels at the exact place of injury in the body was responsible for the symptoms of shock and this conclusion is embodied in the theory of local fluid loss to provide the basis of shock. But this has been subsequently questioned.

As regards the treatment of shock caused by bleeding, there are two stages. In the initial stage, restoration of blood volume by the transfusion of blood or any of its substitutes will raise the blood pressure to normal levels. The blood vessels are responsive to stimuli, in this condition. This phase in the state of shock is known as the reversible stage. But if such a measure as transfusion is of no use, as occurs in late stages of shock on account of neglect or delay due to any cause, the symptoms are irreversible and this stage is hence known as the irreversible stage. It is possible that continuing haemorrhage or infection of injured parts may make the shock appear irreversible and if these are effectively controlled, shock might be reversible. Shock cannot be considered irreversible unless these measures also fail. The reduction in the blood supply to the intestines makes them more permeable to toxins normally not absorbed and also the inability of the liver, in the absence of adequate blood supply, to detoxicate such absorbed toxins, may contribute to the accumulation of endotoxins which aggravate the condition of shock and make it irreversible.

A chemical basis for the occurrence of the two stages, has been advanced. In the beginning, two substances with antagonistic actions appear in blood — VEM (Vaso-excitatory material) released from the renal tissue and VDM (Vaso-depressor material—shown to be none other than ferritin) from the liver. In the reversible stage, VEM is effective, but VDM is rapidly made inert by an enzyme in the liver. VEM makes the vessels sensitive to neural or chemical stimuli so that in the early phase, compensatory mechanisms to offset fall in blood pressure, can be effective, with the result that coronary, cerebral and pulmonary circulations

are not affected much. In the irreversible stage, the enzyme system fails and VDM accumulates in the body and brings about peripheral vasomotor depression and the compensatory mechanisms fail. The role of VEM and VDM is to be confirmed in man. While, as regards haemorrhagic shock, there seems to be the two above mentioned stages, in traumatic shock without bleeding, the first stage may be absent altogether and thus transfusion may be futile from the very beginning. This suggests that some factor other than mere fluid loss, is operative in traumatic shock. Irreversible damage to vital cells may be an underlying cause. A lack of cortical hormones may be a concurrent or contributing factor in the onset of shock in some cases.

The involvement of the nervous system in the production of shock has been demonstrated by experiments in which adrenaline has been given in the form of a very slow infusion. A fall in plasma volume was seen. This was attributed to the increased permeability of the capillaries on account of asphyxia resulting from prolonged vasoconstriction in the splanchnic and cutaneous vessels. The marked dilatation in the vessels of the skeletal muscles also brings about transudation of fluid into the intercellular spaces. In traumatic shock, afferent impulses from the site of injury are thought to excite the sympathoadrenal system and thereby bring about the symptoms of shock, just as in the studies with adrenaline.

The treatment will have to attack the cause as well as take care of the symptoms. Transfusion of blood or its equivalents, keeping the patient warm, allaying the anxiety and the worried condition and even administering adrenal cortical hormones are some of the major modes of tackling this condition.

Shock has been observed after the application of a tourniquet around a limb for prolonged periods. Symptoms appeared immediately after the tourniquet was released.

The cause of shock of coronary ischaemia and pulmonary embolism seems to be the marked and sudden fall in cardiac output and not a reduction in circulating volume.

In secondary shock resulting from burns, haemoconcentration is a marked feature. A major portion of the plasma is lost. The blood becomes very viscous. Regarding the role of toxins, the picture is not very clear. Histamine may not be responsible for the shock of burns. Administration of plasma in large quantities is very effective.

HEART FAILURE

Cardiac failure can either be sudden (acute) and severe or gradual in onset and of a mild or moderate degree. The former type occurs when there is an occlusion (blockage) of a coronary artery or on account of a restriction placed on the movements of the heart as by fluid in the pericardial sac or even due to fibrillation of the ventricles. The cardiac output falls steeply and so also the arterial blood pressure. The venous channels get filled with blood, unlike in shock (see elsewhere).

In the presence of long standing disease, the myocardium is so weakened that it is not able to contract forcibly enough to eject blood from the chambers, especially the ventricles. In most cases of chronic heart failure, the cardiac output is lowered, though this need not always be so. For the same degree of diastolic filling of the chambers, the diseased heart pumps out less amount of blood than a normal one. In other words, the response of the ventricles of the affected heart does not keep pace with the increase in filling pressure. The heart in failure does not obey Starling's law of the heart. The Cardiac reserve — the amount by which the output can be raised maximally when there is a necessity — is definitely diminished in comparison with a normal heart and this is an important finding in cardiac failure. Usually, when the cardiac output is reduced, circulatory adjustments are made to offset the fall in the output. When the amount of blood ejected from the ventricles falls very short of the requirements, compensatory mechanisms fail. Even if the left ventricle alone fails first, inevitably the right one also goes into failure subsequently, as a result of increased load on it. A rise in venous pressure with distension of these vessels is a cardinal feature of congestive failure. Enlargement of the heart is also seen in this condition. Failure of the heart occurs when the

heart has been contracting against a high systemic arterial pressure (hypertension) over a prolonged period or in the case of the heart with defective (incompetent) valves, as in rheumatic disease of the heart with the myocardium also being affected. In certain other diseases like hyperthyroidism, cardiac failure may occur as a complication.

The most frequently seen symptoms of cardiac failure are — venous engorgement with raised pressure; increased blood volume and extracellular fluid volume; water logging of tissues and hence oedema; enlargement of the liver and the spleen; collection of fluid in the serous cavities of the abdomen and thorax; fall in the cardiac output, though rarely, it may be raised. In cases of left ventricular failure, pulmonary congestion and oedema will also be seen.

The occurrence of pulmonary congestion and venous engorgement was formerly attributed to a damming back effect by a failing left ventricle in the case of the former and an inefficient right ventricle in the case of the latter feature. This view is now given up. These effects are now held to be due to a rise in the blood volume which results from a reduction in renal arterial flow. The release of aldosterone adds on to the effect of diminished glomerular filtration rate. Sodium and chloride are retained to a much greater extent and as a result thereof water retention is caused. All these factors bring about a great increase in the body water content and blood volume.

In a small percentage of cases, the cardiac output is elevated. In these subjects, the peripheral resistance is very low, in contrast with the majority of cases of cardiac failure. It is this feature that is taken to be responsible for the raised cardiac output. Arteriovenous shunts, beri-beri and anaemia are some conditions in which high output failure is seen.

Enlargement of the heart, especially of the left ventricle, when the right ventricle is functioning properly, may be a sequel to the greatly increased blood volume, in congestive failure. Pulmonary congestion and oedema which are seen in left ventricular failure, cause dyspnoea, especially in the recumbent or lying posture. Assumption of the sitting or even the standing position, lessens the respiratory distress.

DIGESTION

An animal obtains its energy, as well as materials necessary for the maintenance of its life and growth in young age, from food which it ingests and oxygen which it breathes in. The series of transformations by which food as it occurs in nature and after it is cooked (in the case of human beings), is rendered fit for being processed by the metabolic machinery of the body, has been known as digestion. Food, as it is eaten whether cooked or raw, cannot be absorbed as such from the alimentary canal without being converted to a suitable form. Carbohydrates, fats and proteins are composed of giant-sized molecules, much too large for being assimilated into the blood vessels and lymphatics surrounding the alimentary canal. Digestion, essentially consists of large food molecules being broken down into smaller ones by enzymatic action. Also, the movements of the alimentary canal which propel food from the mouth to the large intestine to be gradually digested and absorbed and to finally eliminate the undigested residue, have been considered along with chemical processes in this section.

DIGESTION IN THE MOUTH

Chewing the food is an act accomplished in the mouth by biting off by incisors, tearing by canines, and grinding by molars, aided by the tongue and cheek muscles. Concomitant with this goes on the salivary action on the contents of the mouth. Saliva is the secretion of three pairs of salivary glands — the parotid, the submaxillary and the sublingual. The parotid gland is situated on the side of the face, below and in front of the ear. It is a racemose gland like the other salivary glands but it secretes a serous or watery type of fluid. Its duct (Stensen's duct) opens into the mouth opposite the 2nd upper molar tooth. The submaxillary gland lies inner to the ramus of the mandible and its duct (Wharton's duct) after running a forward course, opens at the summit of an elevation in the floor of mouth on the side of the frenulum of the tongue. This gland is responsible for a mixture of serous (mainly) and mucous secretions. The sublingual glands lie in the floor of the mouth under the mucous

membrane. A number of ducts (of Rivinus) open into the mouth. The sublingual gland secretes a thick viscid mucous type of secretion.

The salivary gland is made of lobes, each of which consists of lobules which in turn comprise acini. The parotid acinar cells are heavily staining with zymogen granules in them. The mucous secreting cell is pale staining and has secretory granules. In the mixed type of gland (submaxillary), the mucous elements occupy more space in the acinus, the serous secreting cells are in the periphery forming a crescent-shaped structure known as the demilunes of Gianuzzi. Surrounding the alveoli or acini but within the basement membrane of the epithelium, are found the myoepithelial cells which are contractile in nature and can squeeze out the contents of the alveoli. They are seen surrounding the ducts also.

The salivary glands are innervated by both the divisions of the autonomic nervous system. The rostral part of the salivary nucleus (which extends from the glossopharyngeal nucleus to that of the sensory part of the facial nerve) sends fibres through the facial nerve, lingual nerve and chorda tympani, to connect up with the submaxillary ganglion which furnishes fresh fibres to innervate the maxillary and the sublingual glands. The caudal part of the nucleus sends fibres which pass through the glossopharyngeal trunk to the otic ganglion where relaying of fibres takes place and these terminate in the parotid gland. These fibres constitute the parasympathetic nerve supply to the three salivary glands. Stimulation of these fibres will provoke a profuse watery secretion as well as vasodilatation in the gland substance. The sympathetic nerve (preganglionic) fibres arise in the lateral horn cells of the first and second thoracic segments of the spinal cord and pass on to the superior cervical ganglion through the paravertebral sympathetic chain of ganglia. Post-ganglionic fibres travel in the peri-arterial plexus of the external carotid artery to reach the parotid and other glands. Sympathetic action brings about a viscid secretion as well as vasoconstriction in the glandular vessels.

There has been quite a controversy as regards the role of these autonomic fibres in the regulation of the secretory activity

of these glands. Heidenhain attributed a secretory role to the parasympathetic fibres and a so-called 'trophic' action to the sympathetic fibres. Langley and others contested this view and were of the opinion that the parasympathetic fibres were secretory and vasodilator in action, bringing about a thin secretion of large volume. By causing vasoconstriction, sympathetic stimulation reduced the output of saliva which became viscous in character. Rawlinson concluded that the chorda and the glossopharyngeal fibres were given off to the mucous secreting cells and the sympathetics to the serous elements. This, in its turn, has been questioned by Lundberg and others who have provided evidence for the double innervation of each type of salivary cell. To complicate the controversy, there are species differences, say, between the dog and cat, in their responses to stimulation of autonomic fibres.

The formation of saliva in the acini of the glands is an active process requiring the expenditure of energy. Organic substances are added by this activity, to the secretory fluid. The cells forming the walls of the glandular ducts are also concerned with the secretion.

Composition of Saliva: This is changeable. The daily output of saliva is about a litre or more, the rate being highest at meal time. The submaxillary glands account for 70% of the output and, almost completely, the rest of the volume is from the parotid, the sublingual being responsible for as little as 5%. 99.5 % of saliva is water and its specific gravity is between 1002 and 1012. The fluid is ordinarily, slightly hypotonic in respect of blood plasma. The reaction is slightly acidic. (pH — 6 to 7, average 6.4). The earlier estimates giving higher pH values (of actual alkalinity) did not take into account the loss of CO_2 from saliva. The bicarbonate and phosphate in saliva buffer against pH changes. Attempts to acidify or alkalise the saliva with acids and alkalis, in fact, bring about opposite changes, though temporarily. The chloride ion in saliva is important in that, it activates the salivary enzyme ptyalin which is the main organic constituent of this fluid. A mucoprotein is an important constituent of the secretion of the submaxillary gland. Amino acids, urea and uric acid are also found in saliva. Lysozyme is another

enzyme present in saliva. Its action against some bacteria may be protective. Kallidin, a vasodilator polypeptide and the blood group specific substances are the other constituents of saliva.

Regulation of salivary secretion : There is a constant secretion of saliva in small amounts (spontaneous secretion) and is meant to keep the interior of the mouth and the throat in a moist and healthy condition. This type of secretion may be due to the constant release of small amounts of acetyl choline from the parasympathetic nerve endings which activates the glandular cells. Atropine does not abolish this. Metabolic poisons inhibit it. During sleep, the secretory rate is low.

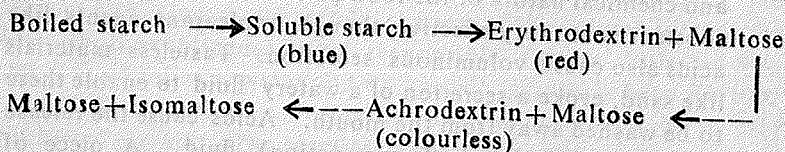
It appears almost certain that nervous control is the only form of regulation of salivary secretion. Secretion in large amounts is brought about reflexly either by the actual presence of food in the mouth and by the excitation of the taste and other receptors in the mouth (unconditioned reflex) or by the excitation of other sense organs (conditioned reflex). Both reflexes usually play a part in effecting a profuse secretion.

- a) Unconditioned reflex — The quantity and the composition of the saliva secreted depend on the physical characteristics and chemical nature of the food placed in the mouth. Tasty substances are very effective, though unpleasant agents like acids also cause voluminous secretion. Tasteless materials like sand, evoke a secretion of a watery fluid to enable these to be washed away from the mouth. Acids cause the release of protein rich (for buffering action) fluid. A piece of meat in the mouth brings forth a thick mucous type of secretion to coat the meat and enable swallowing. Movements of the jaw, as in mastication (chewing) and the manipulations of the dentist bring about the outpouring of saliva—stimulation of afferent nerves (taste fibres of 7th and 9th nerves as well as 5th cranial nerve) in the mouth is what actually occurs in these cases. Similar effects can be brought about even by electrical or natural excitation of various afferent nerves in the oesophagus and even nasal mucosa.

- b) **Conditioned reflex** — The mere sight of attractive and palatable food is a powerful excitant for this reflex. Even the ringing of the dinner bell can act as a stimulus.

It is possible that different parts of the salivary centre are excited by the various forms of stimuli, so that the quality and volume of the saliva may be appropriate to the excitant.

Functions of Saliva : a) As a digestive juice the saliva is perhaps the least important, as its action is of very short duration, food remaining in the mouth for a very short time. The continuity of action of the salivary amylase in the stomach is not likely, since the high acidity of the gastric juice inactivates the enzyme. However, in those portions of the bolus which do not immediately come into contact with the acid secretion of the stomach, salivary action may continue for a while. Salivary amylase is effective in hydrolysing only boiled starch, the action proceeding to the stage of maltose and isomaltose, both of which may be further split by maltase (present in traces in saliva) to yield glucose. The various stages in the digestion of saliva can be observed by treating the products with iodine, the different colours seen indicating the stages of digestion.



Boiling of starch ruptures the cellulose covering of the starch granules which are now susceptible to the action of the salivary enzyme.

- b) Several substances are excreted in the saliva. Cyanide radicles are converted to nontoxic thiocyanates and appear in the saliva. Drugs like morphine and some antibiotics are lost from the body through saliva. Lead, in chronic cases of poisoning, are deposited in the gums of teeth where it

forms a dark visible line, blue in colour. The tartar on the teeth is only sulphur in an organic form. Microbes causing certain diseases like poliomyelitis and rabies are shed from the body in saliva in active sufferers of these diseases. Some people secrete the blood group specific substances in their saliva.

- c) Saliva is necessary for the perception of taste, as it dissolves the various substances in food and these stimulate the taste buds only when they are in solution. This is referred to as the solvent action. Taste appreciation is absent when the mouth is dry. As pointed out earlier, saliva keeps the mouth in a clean and healthy state. When the mouth becomes dry, as in fever, it becomes a site for bacterial decomposition and a foul condition of the mouth results. Organic material (sordes) cover the teeth, tongue and lips so as to necessitate the cleaning of the mouth.
- d) Saliva is also needed for proper articulation of words. The movements of the tongue and lips are hindered in the dry state. Public speakers sip water frequently to avoid the drying up of the mouth by evaporation of saliva while speaking at length.
- e) The state of the water content of the body is reflected in the volume of saliva secreted. Dehydration arising from any cause, reduces the output of saliva and the consequent dessicated condition of the mouth warns of the necessity to replenish the body water store by drinking water.
- f) Swallowing a bolus of food requires proper lubrication of it by a coating of saliva. When salivary secretion is scanty, it is rather difficult to swallow food and drinking of fluids will facilitate deglutition.

Rarely, a permanent suppression of salivation (aptyalism or Xerostomia) may occur as a congenital disorder in which mal-development of salivary glands and their ducts may occur. Temporary diminution of salivary secretion may take place in states of dehydration and fever. Atropine and the belladonna group of

drugs suppress salivation for a few hours. Salivary output may be increased (Siallorrhea) in a number of conditions. Pregnancy is a well recognised cause of this condition. Hypersalivation and nausea are warning signs of impending vomiting.

GASTRIC DIGESTION

The stomach (Gaster for the belly) is the widest part of the alimentary canal and serves as a receptacle for the food eaten at a meal. The oesophagus or the gullet is a conduit or tube connecting the mouth and the pharynx with the stomach. The lining mucous membrane of the oesophagus — stratified squamous epithelium — gives place to a different type at the oesophago-cardiac junction, the demarcating line (Z-Z line) between the two being irregular.

A well developed muscularis mucosae separates the thick muscular tissue of the gastric wall from the innermost layer of mucous membrane which is thrown into folds or rugae. These disappear or are flattened out when the stomach is filled with

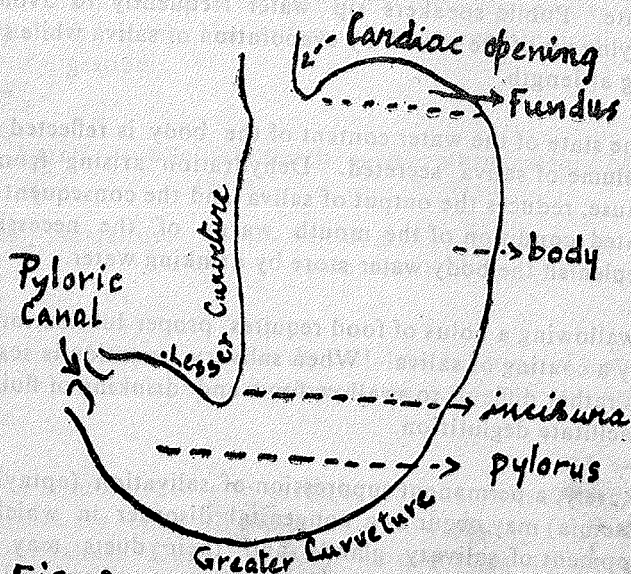


Fig. 20 The STOMACH

food. When the covering of mucous is removed, numerous point-like openings (foveolae) of the gastric glands are revealed and each one of these serves as the common mouth for a few or even several tubular glands. The columnar epithelium which is seen on the surface of the mucous membrane is in continuity with the lining of the glands. The secretory products of these glands vary in quality from one region of the stomach to another. Thus the stomach is divided into the cardiac, fundic and pyloric (Fig. 20) areas. The cardiac zone surrounds the opening of the oesophagus into the stomach. Here the glands are short and tortuous, with mucous secreting cells forming the only elements of importance in them. A very small number of pepsin-secreting cells may also be seen. The fundus part of the stomach is the largest of the three in the stomach, lying between the cardiac region above and pylorus below. The last two are separated from each other anatomically by the incisura angularis, a notch in the lesser curvature of the stomach. Histologically, however, there is no abrupt change from one kind of glands to another. The junction is called as transitional zone showing a gradual change from the fundic glands to that of the pyloric type. The fundic glands are the best developed of the gastric glands and are tubular in shape, the blind end of the gland known as fundus, and the main portion, as the body. The neck connects the long body to the isthmus which in its turn opens into the crypt or the foveola shared by a few other glands. The crypts are as many as a hundred per sq. mm., the gastric glands numbering to a huge total of 35,000,000. The majority of the cells of fundic glands are known as the chief cells, concerned with the synthesis of pepsinogen, the major enzyme of the digestive juice of the stomach. Rennin may be another product of these cells in the calf gastric glands. Gelatinase with a specific and powerful action on gelatin, is another enzyme put out by the chief cells which may be of a single type. Situated between the basement membrane of the gland and the chief cells are the oxyntic (parietal) or acid secreting cells. These give rise to a wavy outline to the overall shape of the fundic gland. The hydrochloric acid elaborated in these cells is passed on to the lumen of the gland by means of sub-microscopic (seen under the electron microscope) intracellular canaliculi whose walls present a brush border formed by microrilli which are characteristic of cells capable of active transport.

of materials against a concentration gradient. Such a structure is also seen in the renal epithelium of the proximal convoluted tubule. The oxyntic cell has been seen to undergo structural changes when it is stimulated by any one of the usual means — histamine, insulin hypoglycemia or vagal excitation. The microvilli increase in number so as to completely occupy the space of the canaliculi and thereby presumably, the acid secreting area is increased enormously. Vesicles distributed haphazardly in the cell get congregated near the canaliculi. These features are not seen in all the parietal cells, of which only about three fourths are excited at any one time, by any of the usual agents. Acetazolamide which inhibits carbonic anhydrase prevents these changes, giving support to the ideas on “the physico-chemical basis of acid formation.”

The gastric glands possess double innervation. The pre-ganglionic sympathetic fibres arise from the lateral horns of the 5th — 10th dorsal spinal segments of the spinal cord and after passing through the paravertebral sympathetic chain without synapsing, end in the ganglia of the coeliac plexus. Fresh fibres arise here and are conveyed to the walls of the stomach through the arterial plexuses. Afferent fibres follow a similar course, but enter the cord through the dorsal roots. The parasympathetic fibres are conveyed in the vagus on both sides, the right nerve providing preganglionic fibres to the posterior surface of the stomach and the left one, to the anterior surface. The vagal fibres mingle with those of the sympathetic and are conveyed together with the blood vessels to the muscular stratum of the stomach wall, to synapse with the ganglion cells of the myenteric plexus of Auerbach and the Meissner's plexus below the mucous membrane. Short post-ganglionic fibres are given off to the glands of the stomach. The vagal fibres promote the secretory activity of the glands as well as the release of gastrin, the hormone of the stomach, from the gastric antrum. Pepsin-rich and highly acidic secretion results from vagal stimulation. Acetyl choline is the nerve transmitter which excites the glands and atropine blocks this action. The glands of the lesser curvature are more susceptible to vagal stimulation and produce a juice of great digestive power. This explains the greater incidence of ulcers in this part of the stomach. Sympathetic stimulation

leads on to an alkaline mucous secretion, especially from the pylorus. Vagal stimulation excites the surface epithelium and the neck cells of the fundic region, to secrete mucin. The role of the sympathetic fibres with respect to the fundic glands has not yet been elucidated, though an inhibitory action is suggested.

Composition of gastric juice: The constituents of this fluid are the products of the secretion of different types of gland cells and the composition is highly variable. The parietal cell is believed to secrete acid of a constant strength, but it can vary its rate of secretion. The peptic cell secretes a fluid at constant rate, but the concentration varies. The acidity of the juice depends on the rate of secretion of the oxyntic cell. The details concerning the gastric juice are as given below.

Daily output	1200 — 1500 ml.
Sp. gr.	1002 — 1004
Acidity of fasting juice	40 — 60 m Eq./litre
pH	0.9 — 1.2.

<i>Constituents:</i>	a) Inorganic	— Hydrochloric acid Bicarbonate Sulphate, phosphate Sodium, Potassium and Calcium.
	b) Organic	— Pepsinogen Lysozyme, gelatinase, Urease. Carbonic anhydrase Intrinsic factor of Castle and blood group substances. Mucin

Mechanism of HCl secretion: It has been widely, though not by all, accepted that the oxyntic cell is responsible for the secretion of hydrochloric acid. It was Pavlov who put forward the view that the parietal cell secreted acid of a constant concentration but that it could vary the rate of the output. The modern concept of the mechanism underlying acid secretion is

that of Davenport who concludes that the hydrogen ion is provided by an active metabolic process from glucose and water. The hydroxyl groups which are the by-product of the dissociation of water in giving off H ions are neutralised by the H ions which accumulate as a result of the action of carbonic anhydrase in the cell. The Cl^- is actively transported from blood and through the cell matter into the canaliculus in which the H ions and the Cl^- are coupled to form hydrochloric acid. Bicarbonate ions which arise out of the action of carbonic anhydrase diffuse into the blood stream and eventually bring about the alkaline tide of urine in the gastric digestive period. Diamox, a sulphonamide drug, abolishes acid secretion totally or nearly totally by inhibiting carbonic anhydrase.

Action of the digestive enzymes in brief:

1. Pepsin is the major protein splitting enzyme of the gastric juice. Its precursor exists in the substance of the chief cell in the form of zymogen granules which become reduced in number after the cell has been excited. The inactive enzyme which is released into the lumen of the gland is known as pepsinogen (molecular weight 42,000). In an acid environment of pH below 6, it is activated autocatalytically to yield the digestive enzyme pepsin, a protein, of molecular weight 35,000. Pepsin is most effective around a pH of 2.0 and is almost completely inactivated above a pH of 5. It *breaks the protein linkages* which bind amino groups to the aromatic amino acids, carrying digestion to the stage of *proteoses and peptones mainly*. A few amino acids and polypeptids may also be split off incidentally, from the original protein molecule. Sham feeding and experimental vagal stimulation increase the output markedly. Parasympathomimetic agents stimulate pepsin secretion. Histamine has no such effect. Pepsin is even found in blood and its derivative uropepsin, in the urine.

Other proteolytic enzymes of much less activity are:—
 Cathepsin with optimum pH at 4, Gastricin most active at pH 3 and possibly others.

Rennin, the milk curdling enzyme which has been prepared from the gastric juice of the calf with an optimum pH at 6–6.5 for its action, has not been found in human gastric juice (in which it will be inactive, if present) wherein pepsin substitutes for it. The act of curdling consists of a splitting of milk casein into a soluble whey protein (a proteose) and paracasein. The latter, in combination with calcium ions, forms Calcium Paracaseinate which is insoluble and known popularly as a curd and this further undergoes peptic digestion.

The occurrence of a gastric lipase is very unlikely and if there be a fat splitting enzyme in the gastric juice, it could be due to regurgitation of the pancreatic juice from the duodenum. The high acidity of the stomach precludes its being effective.

Gelatinase is another enzyme found in gastric contents and it is much more powerful than pepsin, in its action on gelatin.

Hydrolysis of cane sugar (sucrose) possibly occurs on account of the action of hydrochloric acid on the sugar.

Mucus in the stomach: The surface epithelium secretes 'visible mucus' which forms a thick viscous and jelly like coating on the mucosal surface. Irritation of gastric lining, mechanical or chemical (alcohol, pungent substances and spices) provokes the secretion of this type of mucus, which protects the mucous membrane.

Soluble mucus is secreted by cardiac and pyloric glands, as a response to sympathetic stimulation and has a buffering effect against the acid secretion. Mucin is a glycoprotein and it inhibits digestion by pepsin. It has a protective function.

Regulation of Gastric Secretion: Pavlov, the Russian Physiologist, contributed much to the advancement of the knowledge in this field. He devised a method to collect pure gastric juice without admixture with food. Out of the stomach a separate pouch (Fig. 21) was created, which had both nervous and vascular connections with the rest of the stomach, but the cavity of the pouch had no communication with that of the main part of the

stomach. A fistula (communication or passage from the pouch) was made to enable the collection of such juice as was secreted in the pouch. Heidenhain prepared another kind of pouch which had only vascular connections with the main body of stomach, the nerve supply to the pouch having been sectioned. Pavlov's pouch facilitated the study of gastric secretion brought about by nerve induced mechanisms, whereas Heidenhain's pouch made it possible to observe purely hormonal or chemical influences on gastric secretion, since there were no nerve fibre

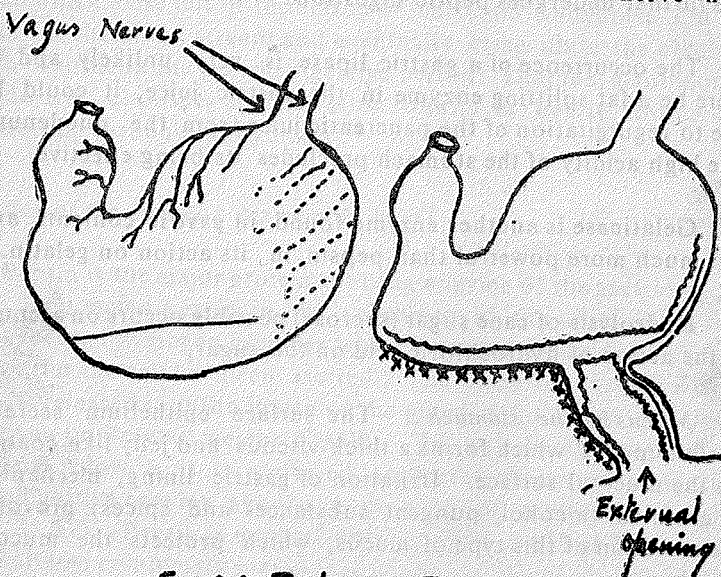


Fig.21 Pavlov's Pouch

connections. Other workers like Ivy have made certain modifications in the surgical procedures, thereby obtaining a transplanted (denervated) pouch away from the stomach region. By means of these devices, it has been possible to make a detailed study of the phases of gastric secretion. Most observations have been made in the dog by Pavlov and others and they have been assumed to hold good in the case of human subject. In the dog, gastric secretion is pronouncedly intermittent, while in man, there seems to be a constant or basal secretory activity which becomes accentuated at meal time and thereafter, for a certain period. Otherwise, the results of the experiments on the dog can

hold good even in the case of the human subject. From the forementioned investigations of several workers, it has emerged that secretion of gastric juice occurs in three phases or 'bouts' in a definite order which are named the psychic or cephalic phase the gastric phase and the intestinal phase.

Psychic or Cephalic phase : The mere sight, smell or taste of food evokes a secretion of gastric juice in anticipation of the 'arrival' of food in the stomach. Some authors distinguish between the psychic and the cephalic phases. It is held by them that the stimulation of telereceptors (receptors excited by stimuli arising at a distance) by sight of food (vision) or smell (olfactory receptors) gives rise to psychic secretion, while the actual presence of food in the mouth, by stimulation of the taste buds (gustatory receptors), initiate the cephalic phase (initial reflex phase) and the resulting juice secreted being named as appetite juice. It is possible that because of a strong psychic element, human gastric secretion may go on constantly at basal level. The existence of a cephalic phase in the dog was established by Pavlov, by means of the "sham feeding" experiments. A dog had an opening made (surgically) in its abdominal wall and also in the stomach wall so that the organ communicated with the exterior. An

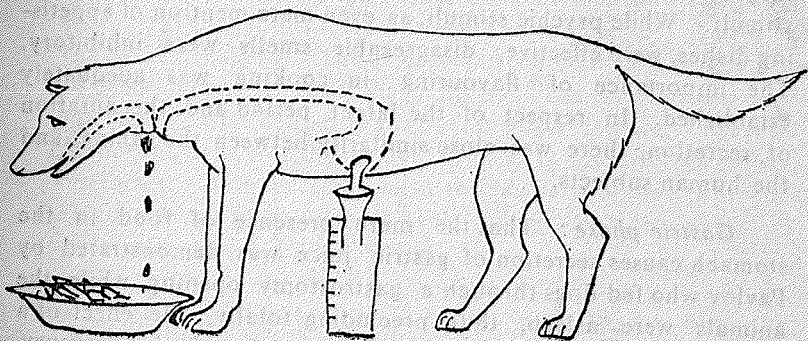


Fig. 22 Sham Feeding

opening in the wall of the oesophagus (oesophagostomy) prevented the food which was chewed and swallowed, from reaching the stomach but let it fall out (Fig. 22). If the two vagi nerves were intact, a profuse reflex secretion was produced in the pouch and was collected in a receptacle placed under the abdomen. If the vagus were cut on both sides, no secretion occurred, proving that the mechanism underlying this mode of secretion is purely nervous (reflex) in origin. The latency for this reflex phase was a few minutes but the effect lasted for more than an hour. The juice was strongly acidic and had a high pepsin content. Vagal stimulation, electrically, produced a similar effect, further demonstrating its involvement in the cephalic phase. The point to emphasize in this connection is that food need not actually enter the stomach in order for it to bring about a secretion.

Carlson extended Pavlov's studies on the dog, to the human subject. In the place of an oesophageal opening, as in the dog the subject who had a gastrostomy performed for a constricted oesophagus, was instructed to spit out food after it was well masticated so that the entry of food into the stomach was prevented. When sweets and fruits were chewed, the secretion was large in volume. Even the sight and smell of food were effective stimuli. While psychic stimuli, as even mere mention of appetising dishes, were effective, disagreeable smells were inhibitory. The importance of flavouring in cooking was adequately established. In respect of the latent period and the duration of secretion, there was close similarity between the canine and the human subjects.

Gastric phase: That the mere presence of food in the stomach causes secretion of gastric juice was demonstrated by Pavlov who fed dogs through a gastrostomy opening while the animals were asleep, thus precluding totally, the effect of a cephalic phase. Edkins, in the first decade of this century, prepared an extract of the pyloric mucous membrane, which on injection into an animal, excited gastric secretion and the extract was thought by him to contain a gastric (more properly pyloric or antral) hormone, "gastrin" which according to Edkins, was produced when food came into contact with the lining of the pyloric antrum. Gastrin is a protein or polypeptid substance,

long mistaken for histamine. It seems to be a specific excitant for gastric secretion, since histamine-free extracts of pyloric mucous membrane are effective. Further, gastrin does not cause fall in blood pressure while histamine causes vasodilatation. Histaminase, the enzyme which destroys histamine, has no action on gastrin.

In spite of what has been assumed as the basis of gastric phase, as explained in the paragraph above, it seems certain that the vagus plays a role in gastric phase also, since in a denervated stomach (vagus divided on both sides), the gastric phase (induced by purified gastrin) produced only acid-rich secretion like that in response to histamine and not one of high peptic power also. Babkin and Linde advanced the view that both acetyl choline (vagal stimulation) and gastrin caused the release of histamine near the oxyntic cell. Ivy showed that histamine brought about the liberation of hydrochloric acid from the stomach glands.

The excitation of the pyloric mucosa by the chemical constituents of food materials — meat extracts, soaps formed from fats in the food, as well as its irritation mechanically by food or even by indigestible substances introduced into the stomach, produced local reflexes involving the Meissner's plexus with its central and peripheral connections, resulting in the release of gastrin from the pyloric mucosa. Thus, gastrin seems to be a product both of chemical and nervous mechanisms. The conclusion now is inescapable that neither the cephalic phase is purely nervous in its mechanism, nor the gastric phase is purely hormonal in character. Both elements seem to feature in the two phases. Gastrin seems to be released even in the cephalic phase as a consequence of vagal excitation.

The basis of treatment of peptic ulcer by a two-pronged approach, namely double vagotomy and subtotal re-section (especially of the pyloric antral region) of the stomach, appears to be a sound one, in that, both nervous and hormonal effects concerned in gastric secretion are sought to be minimised.

Further, it is the view of several workers that the pyloric mucosa not only elaborates an excitatory substance, the gastrin,

but also an inhibitory agent, when the contents of the stomach which are acidic, come into contact with it. This points to an automatic or built-in self regulatory control of gastric secretion.

The intestinal phase : Babkin found that some food substances when placed in the intestinal canal, promoted gastric secretion. The following substances were potent in this respect—products of meat digestion, milk etc. The onset of secretion was somewhat slow but it continued for several hours, the type of secretion being one of much lower digestive power. The exact relationship that this mode of secretion has to the earlier phases has not been understood. So also is the cause of this. Most probably, a chemical mechanism is involved. A complicating factor is the inhibitory effect on gastric secretion brought about by the presence of certain materials like fat, in the duodenum. A hormone, enterogastrone, is released and this depresses gastric secretion. Fat, in contact with the intestinal mucosa, makes it release a substance (enterogastrone) which, when carried (in the blood stream) to the gastric glands, suppresses gastric secretion as well as the motility of the stomach wall. A derivative of it or it itself is found in the urine and exhibits a similar depressant action. It is named urogastrone. The chemical nature of enterogastrone is yet to be elucidated.

Histamine : The importance of histamine as a powerful stimulant for gastric acid secretion was revealed from the work of many investigators who were concerned with the real identities of gastrin and secretin. Gastric response resulted when histamine was produced in the body itself or was administered. A very small dose 0.2 mg or so provoked a secretion of hydrochloric acid in human subjects. It is a useful agent in distinguishing between the two kinds of achlorhydria. In one case (false achlorhydria) hydrochloric acid is secreted in response to histamine and in the other, there is no response at all (histamine fast or true achlorhydria). The latter condition is seen in pernicious anaemia.

Collection of gastric juice : This can be done by means of the Ryle's tube, which is about 18 inches long and half a centimetre in diameter and is made of rubber. The blunt closed end

is weighted, so as to facilitate swallowing. There are holes in the sides of the tube to enable stomach secretions to enter the tube. A syringe is attached to the open upper end and gastric contents can be aspirated. There are marks made on the tube to indicate the extent to which the tube has been introduced into the oesophagus and stomach.

The details concerning the analysis of gastric juice fall outside the scope of physiology, by definition. Works on Biochemistry may be referred to, for these.

In the early nineteenth century, the Canadian Physician, Beaumont, studied the effects of emotional states on the stomach secretion in Alexis St. Martin, a Canadian who survived a gunshot injury in the abdomen which resulted in a gastric fistula. Beaumont observed the gastric mucosa under different states of fear, rage and anxiety. He concluded that gastric secretion was profoundly affected in these conditions. Wolf and Wolff extended these studies in the forties of the present century and confirmed the observations made on St. Martin. The hypothalamus is undoubtedly implicated in the various responses.

THE PANCREAS

This is uniquely two glands in one. The exocrine gland puts out the so-called pancreatic juice composed of some of the most powerful of digestive enzymes in the alimentary canal. In fact, it can be said, that pancreatic digestion is adequate to deal with food materials and take on their conversion to the subsequent stages even in the absence of gastric enzymes. Gastrectomy does not materially affect the digestive processes. The pancreas is developed as two off-shoots of the primitive embryonic alimentary canal. The dorsal of the two, gives rise to the major portion of the gland. The ventral one is associated with the diverticulum which forms the liver, later on. The two parts of the pancreas fuse near the second part of the duodenum into which they empty their secretions through the sphincter of Oddi along with the common bile duct. The pancreas is described as consisting of three parts, a head, a body and a tail, running in a transverse direction from near the duodenum, leftwards.

The histological design of the gland is very similar to that of the salivary glands. The gland is divided into secondary lobules, each having a separate branch of the pancreatic duct and easily separable from others, since it is well demarcated by connective tissue. In its turn, each secondary lobule consists of a number of primary lobules incompletely delineated. The primary lobule is made up of a number of acini formed by polygonal cells. Interspersed among the lobules are found the islets of Langerhans.

The pancreas is innervated by branches from the vagus and splanchnic nerves. The vagal fibres end in the intrinsic ganglia of the pancreas which give off the post-ganglionic fibres to end on the secretory cells. The sympathetic post-ganglionic fibres emerge from the coeliac plexus and pass to the gland along blood vessels, especially the superior pancreatico-duodenal artery.

The secretory cells of the pancreatic acinus contain intracellular zymogen granules which are the precursors of the enzymes released by the cells. These collect near the luminal end of the cell, ready as it were to enter the duct system.

Secretory activity of the glandular cells: It has been observed that in certain diseases of the pancreas, enzyme secretion may be affected without any change in the volume of the fluid or bicarbonate content and in alloxan poisoning, the reverse occurs. This leads to the conclusion that the acinar cells are concerned with the synthesis of the enzymes whereas the cells lining the ducts (which show degenerative changes) have to do with contributing water and bicarbonate. From stop-flow studies (in alloxan poisoning) similar to those in respect of the kidney, it has been concluded that the water and bicarbonate secreted by the cells of the intralobular ducts, were equilibrated with the plasma—losing bicarbonate partly and gaining in Cl^- concentration as pancreatic juice passed through the interlobular ducts. Carbonic anhydrase is present in the pancreatic tissue—in the cells lining the intralobular ducts but not in acinar cells. It was also seen that there was free exchange of Na^+ and K^+ between the plasma and pancreatic juice, resulting in equality of concentration of these two ions between these two fluids.

The secretion of the enzymes is the function of the acinar cells. Vagal stimulation promotes the synthesis of enzymes. Protein rich diet enhanced enzyme synthesis. The essential amino acids had a specific effect in this respect. The synthesised enzymes exist in the cell as zymogen granules. When stimulated suitably, the cells discharge these granules in the form of enzymes into the lumen of the gland. Stages in the evolution of zymogen granules of protein splitting enzymes have been observed by intracellular studies, using the electron microscope and autoradiography.

Pancreatic juice: The product of the pancreatic acini is a colourless, odourless, watery liquid (isotonic with blood) of high alkalinity due to high concentration of sodium bicarbonate. The daily output amounts to about 6.0 ml. Attention is drawn to the fact that the stomach glands and the pancreas secrete juices of opposite reactions (pH) so that the acid-base balance of the body fluids is not disturbed. The mixing of the two secretions in the intestine in order to avoid marked deviation from the normal pH of the intestinal contents, is another important point to be noted. The sum total of the chloride and bicarbonate concentrations in the pancreatic juice is nearly constant. If one decreases, the other increases.

The enzymes of the pancreatic juice are effective against all kinds of food — carbohydrates, proteins and fats. They do not require for their action, any preprocessing of food materials, by gastric enzymes though usually they carry on the digestion to a subsequent stage after the preliminary action by the gastric juice.

Proteolytic enzymes: Trypsin and chymotrypsin are the chief enzymes of this category. They are secreted in their zymogen or inactive form — trypsinogen and chymotrypsinogen. Both have been obtained in a crystalline state. Trypsinogen has a molecular weight around 25,000 which, when split, yields trypsin (an endopeptidase), a large polypeptide which is active against even uncooked protein. Its action results in the production of proteoses and polypeptides. The cleavage or split occurs in the peptid linkages well within the protein chain and so the enzyme is an endopeptidase which is active at an optimum pH

of between 8 and 9. Trypsin can bring about coagulation of blood, substituting for thromboplastin. It has a weak action on milk. Trypsinogen is activated by contact with an enzyme, enterokinase, in the intestinal mucosa (see below) or even by acidity or high concentrations of magnesium sulphate. Small amounts of trypsin which results from the activation can bring about autocatalytically, further activation of trypsinogen. In the glandular tissue of the pancreas, it is presumed that some inhibition of this activation exists, in order to prevent a digestive action of the enzyme on the acinar cells themselves. This is suggested by the fact that in crude extracts, activation does not take place. Chymotrypsinogen has also more or less the same molecular weight as trypsinogen. The break up of both the molecules of trypsinogen and chymotrypsinogen during activation seems to occur at the linkage by disulphide bonds 'connecting serine' region with a histidine region. Trypsin in large amounts is the activator for chymotrypsinogen and once chymotrypsin (Π form) results, it autocatalyses the rest of the conversion. It has a marked action in coagulating milk (not on blood, unlike trypsin). It also acts on casein to digest it. Trypsin and chymotrypsin together are even more effective in bringing about digestion of casein than chymotrypsin alone. Chymotrypsin is also an endopeptidase and the optimum pH for its action is the same as for trypsin.

The polypeptids arising out of the tryptic digestion are further acted on by certain peptidases in the intestinal mucosa. The pancreatic juice contains carboxy-peptidase, an enzyme which splits off the terminal amino acid holding the free carboxyl (COOH) group and as such, it is an exopeptidase. Even this enzyme is in an inactive form, needing activation by trypsin.

Ribonuclease and desoxynuclease are also found in the pancreatic secretion and these take part in the conversion of nucleic acids into mononucleotides at an optimum pH of around 7. Of minor importance are elastase (acting on elastin) and collagenase (on collagen).

Fat splitting enzyme: Lipase brings about hydrolysis of fats into fatty acids and glycerol, in the presence of bile salts or even

synthetic detergents and in alkaline medium. This enzyme has not been prepared in the pure state. Heavy metal ions of copper, iron and also the halogens, chlorine, bromine and iodine and paradoxically, even bile salts in high concentration, inhibit the action of lipase. Two types of lipase, phospholipase A and phospholipase B are said to occur in pancreatic juice and they have different actions.

Amylase: This is an alpha amylase, as is the one in the saliva. It has been prepared in the pure state. It carries the digestion of starch and even glycogen to the stage of maltose, in a slightly acid or neutral medium (pH-6.5 to 7.2). Chloride ion is essential for the action of this amylase also and certain neutral salts which form an integral part of the molecule of the enzyme are also necessary in this regard. Pancreatic amylase can act on even raw starch unlike its salivary analogue.

The importance of pancreatic juice has already been stressed and an absence of this secretion from the alimentary canal results in marked disturbance in the digestive process. The persistence of acidity in the intestine may be harmful and fat and protein matter will have to be lost in the undigested and unabsorbed state leading to a condition of steatorrhea—presence of large amounts of fat in the stool.

Regulation of pancreatic secretion: It is established that there is both nervous and humoral control in the regulation of pancreatic activity.

Though the earlier work of Claude Bernard and others indicated that pancreatic secretion occurred only in response to ingestion of food, it is now certain that there is a continuous basal secretion in the case of the pancreas also, since fluid can always be collected through a pancreatic fistula and also through a long rubber tube passed into the duodenum through the mouth.

Neural mechanism — The sympathetic effects vary in that, an increase or decrease of secretory activity may result. Atropine blocks the sympathetic effects, showing that these fibres are really cholinergic. It is possible that the duct system is affected by

sympathetic stimulation by way of constriction and reduction of flow.

Vagal stimulation resulted in the production of a thick viscid juice of low alkalinity, low water content but of high enzyme concentration. Sham-feeding produced a fluid of the same character. Anticholinergic drugs like atropine abolished vagal effects, whereas cholinergic drugs enhanced the secretion of the type resulting from vagal excitation. Stimuli to the stomach wall as caused by distension of the fundus, caused the release of a profuse and enzyme rich secretion. Even section of the two vagi did not prevent this effect. Local nerve plexuses seem to be involved in this so-called gastro-pancreatic reflex.

Chemical control — In 1902, Bayliss and Starling made a great discovery. They prepared an acid extract of the duodenal mucosa which was neutralised and administered intravenously to a dog. This evoked the output of pancreatic juice of high alkalinity and high enzyme content. The term 'hormone' was coined by these workers to refer to any substance which acted as a chemical messenger. The specific name, secretin, was given to the particular substance in the duodenal extract. The concept of a hormone being released in one part of the body and conveyed in the blood stream, to a remote site where it exerted its effect, was thus originated by this epoch-making finding. Secretin which was later obtained in the pure form (m.w.5000) had a stimulating action on the pancreas as well as the liver. The physiological mode of secretin release is as follows: When acid chyme (the contents of the stomach being rendered into a semi-solid mass) passes into the duodenum and comes into close contact with the walls of the duodenum, the mucosa of this region liberates the substance secretin into the blood vessels which convey the hormone to the pancreatic acini in order to excite them. Pure secretin brought about the elaboration of a fluid, highly alkaline, of large volume but low digestive power.

Crude extracts of the duodenal mucosa were prepared by Harper and Raper in 1943 and an attempt was made to isolate a substance which brought forth only on enzyme output from what was left after pure secretin was removed

from the extract. Pancreozymin, another hormone, was detected by these workers. This work was later substantiated by others. Pancreozymin seems to be elaborated by the duodenal mucosa on coming into contact with the products of protein digestion like peptones. Pancreozymin was responsible for the output of pancreatic juice of low volume, viscid nature, high enzyme content but low alkalinity. Transplanted denervated pancreatic tissue responded to pancreozymin administered intravenously.

Under physiological conditions, both nervous and chemical mechanisms are involved in the regulation of pancreatic secretion.

THE LIVER

The ideas regarding the structural organisation of the liver have undergone a drastic revision with the advent of the work of Elias. In the past, for many decades, the liver lobule with its central vein, was thought to be composed of radiating cords (from the central vein) of hepatic cells. Two adjacent cords were thought to enclose a minute bile capillary and immediately next to it was the blood capillary arising out of a portal vein radicle which united with a small branch of the hepatic artery and supplied blood for the hepatic lobule. The hepatic cells along with the Kupffer's cells in the blood capillary of the lobule, secreted and excreted respectively, substances in the bile capillary, their raw materials being furnished by the blood capillary. The bile vessels of the lobule joined each other, giving rise to a small bile duct. Each lobule had its own small bile duct, branch of the hepatic artery and portal vein twig, these three together forming the portal system or triad, one meant for each lobule. Perhaps, the conclusions of the older workers regarding the structure of a liver lobule were based on the two dimensional view as obtained in ordinary histological preparations. Elias has sought to radically revise the current ideas regarding the architecture of the liver. According to him, the basic structure of the lobule consists of plates of one liver cell thickness criss crossing each other, thereby producing a honeycomb-like or sponge-like material. A system of intercommunicating tunnels

or "lacunae" hold the blood vessels (sinusoids) which are lined by the Kupffer's cells. These cells are also seen in the spleen and are starshaped and belong to the widely distributed reticulo-endothelial system and hence are phagocytic in function. The blood vessels or liver sinusoids contain mixed blood derived from the portal vein and the hepatic artery and drain it into the central vein of the lobule which joins other central veins (of other lobules) to eventually form the hepatic vein joining the inferior vena cava. The bile capillaries or canaliculi surround the individual hepatic cells proper and are separated from the blood sinusoids only by a single layer of liver cells. The liver cells have microvilli projecting into the bile passages (seen under the electron microscope) suggesting an active transfer of substances from the cell into the bile passage. The liver cell shows under its boundary with the bile canaliculus, a very complex Golgi apparatus, indicating an active secretory function.

Bile: The bile is mainly the secretory product of the liver cell and also contains the excreted substances like bile pigments arising out of the chemical degradation of haemoglobin. Liver bile is highly alkaline (pH 8 and above). In the gall bladder, the alkalinity is reduced to almost neutrality. The bile salts, bile pigments and certain fatty substances like fatty acids, cholesterol, and lecithin constitute the major portion of the solids of the bile of the liver. The gall bladder concentrates the liver bile by removing water and certain inorganic substances.

The bile salts of human liver bile are sodium and potassium salts of taurocholic and glycocholic acids. Taurine, a sulphur containing amino acid, and cholic acid, a steroid compound, yield taurocholic acid, while glycine along with cholic acid goes into the constitution of glycocholic acid. Cholic acid is obtained both from food and from bodily synthesis. Glycine and taurine seem to be synthesised in large amounts in the body. Bile salts are very carefully conserved and only the small amount lost in the intestines are replaced by fresh synthesis. Most of the bile salts secreted into the intestines along with the bile, is reabsorbed into the portal vein to be carried to the liver and recirculated. However, if bile salts are removed from the liver by artificially draining the bile through a fistula, the bile salt

concentration in the bile is not appreciably lowered. On the contrary, administration of bile salts to raise their level in bile, seems to depress their synthesis in the liver. Thus, there is a regulating mechanism to maintain a constant concentration of the bile salts in the bile. Bile salts serve to facilitate fat digestion and absorption. They lower the surface tension of the contents of the intestines so that emulsification of fats can occur—fats are rendered into very small globules—chylomicrons, less than 0.5 micron in diameter which apparently may be absorbed as such into the lacteals of the intestinal villi. Emulsification of fat enables it to present a large surface area for the action of the enzyme, lipase. In addition, bile salts may enhance the enzymatic action by activating lipase. The fatty acids liberated by the breakdown of fats may form soaps with the alkali of intestinal contents. Bile salts form complexes with fatty acids aiding in their absorption into the capillaries of the villi. Bile salts are also necessary for the absorption of cholesterol. These salts are the only constituents of bile that are useful in digestion and hence in the body economy. All the other bile substances should be considered as fit to be excreted and as of no value immediate or remote, to the body.

Bile pigments: These are—bilirubin which occurs in a much larger amount, comparatively speaking, in human bile and biliverdin occurring in smaller amounts. The former is, as its name suggests, a reddish pigment, the latter a green substance. These are the final degradation products of the stepwise break up of the haemoglobin molecule. The actual sequence of these steps may be found in works dealing with biochemistry. It is doubted whether the reactions in the breakdown *in vivo* are the same as that arrived at by *in vitro* studies in the laboratory. While the iron of the pigment molecule is recircled to synthesise haemoglobin, the rest (excluding the protein part—globin) is finally converted by the reticuloendothelial cells (wherever they are present) to the excretory products, bilirubin and biliverdin. The bile pigments are also recirculated between the liver and the intestines in the manner of the bile salts and this has been referred to in the older text books of Physiology, as the enterohepatic cycle. In the intestine, bilirubin undergoes reduction to urobilinogen by bacterial action and part of the urobilinogen (also called

stercobilinogen because of its presence in faeces) is eliminated in the stool and on coming into contact with atmospheric oxygen, is oxidised to a dark pigment, urobilin (stercobilin). Urobilinogen also is recycled in the enterohepatic cycle. It to a large extent, reconverted to bilirubin in the liver to be re-excreted in bile. Such of it that escapes re-excretion into the bile, passes into the blood and may reach the kidney to be passed into the urine and to be finally transformed to urobilin outside the body. Though urobilinogen could impart a yellow colour to urine, normally the tint of urine is not due to this substance.

The problem of jaundice is deliberately excluded from the purview of this account, as it properly belongs to Biochemistry.

Cholesterol: Cholesterol occurs as such in the bile. The bile salts keep the cholesterol in solution, if the former are in sufficiently high proportion in relation to cholesterol. If the relative strength is less than 13 : 1, cholesterol leaves the solution and precipitates. The formation of gall stones may be accounted for on this basis. The bile cholesterol content is fairly constant and is not dependent on the amount in the blood or in the food. Here again, there seems to be an enterohepatic cycle in that cholesterol of bile is reabsorbed in the intestines to be re-excreted in bile.

The secretory process and the control of biliary secretion: Active transfer of water and organic substances like bile pigments and bile salts, seems to be the basis of secretion. Inorganic constituents may be freely exchanged between the blood and the bile.

Bile production is a continuous process in the liver lobules, though it is more in the waking hours than during sleep. This is because food intake occurs during waking hours. The proteins found in food are effective stimulants for bile secretion. Fats have an uncertain effect and carbohydrates exert an inhibitory effect. Agents which promote bile secretion from the liver are known as cholagogues — which raise the bile output, increasing both volume and the output of solid materials. Bile salts themselves act as powerful cholagogues. Bile salt derivatives like dehydrocholates, increase the volume of bile secreted and such

factors are called hydrocholeretics. Hydrochloric acid, when present in the intestine, evokes bile secretion. It is possible that this effect may be due to secretin which may be released thereby. But the action of secretin regarding bile secretion is doubtful. Secretin may at least act as a hydrocholeretic. A separate hormone which may be released from the duodenal mucosa and going by the name hepatocrinin, may be responsible for raising the bile output. While it may be that nervous factors may also play a role, vagal stimulation, contrary to expectation, has an inhibitory effect on bile secretion. More has to be elucidated about this.

At this juncture, it is useful to have an idea of the large number of functions subserved by the liver. It is notable, how a single type of cell, viz — the hepatic cell, can be responsible for a number of actions. The only other cell with such a versatility is the secreting cell of the breast alveolus. Some authors have wondered whether the various activities of the liver cell may really be due to its ability to influence various chemical reactions at a common point of intersection which thereafter proceed in their own different directions. The net effect may be that the liver cell influences each biochemical pathway individually.

A. *Functions concerned with blood.*

1. Erythropoiesis in the embryo in the hepatic phase.
2. Production of substances needed for blood coagulation—Fibrinogen and Prothrombin.
3. Synthesis of heparin.
4. Storage of erythropoietic factors like vitamin B₁₂.
5. Storage of iron and trace elements needed in red cell formation by the marrow.
6. Synthesis of serum albumin as well as serum globulin.
7. As a reservoir of blood.

B. 1. Metabolic activities related to the disposal of a) Proteins, b) carbohydrates and c) fats, in the body. Incidentally, liver generates heat, serving to regulate body temperature.

2. Storage of vitamin A and vitamin D.

Liver function tests have been omitted as being beyond the scope of this account.

The Gall-Bladder: This is a thin-walled bag-like structure of capacity about 50 ml. The histological elements making up the wall of the gall bladder are, from without inwards — a layer of plain muscle tissue disposed in a loose arrangement of collagenous and elastic fibres, and an inner zone of columnar epithelial cells. The duct of gall bladder (cystic duct) joins the hepatic duct to form the common bile duct. Liver bile enters the gall bladder through the hepatic and cystic ducts. After undergoing certain changes, gall bladder bile is expelled through the cystic duct to flow along the common bile duct and to enter the intestinal canal. The common bile duct gains access to the duodenal part of the gut by passing at an angle through the duodenal wall wherein it is joined by the pancreatic duct to form the ampulla of Vater. A sphincter of plain muscle fibres (sphincter of Oddi) encircles the junction between the ampulla of Vater and the duodenum. The pancreatic duct and the common bile duct also have sphincter-like structures near their terminations at the ampulla of Vater.

The electron microscope has revealed the ultra-structure of the gall bladder mucosa. While there seem to be three kinds of epithelial cells, the most common of these has a structure characteristic of absorptive function—microvilli and internal characteristics.

The functions of the gall bladder — It has been established that the gall bladder is not absolutely essential for digestive processes. Its removal does not have adverse effects. In the main, reduction of the water content (concentration) and absorption of inorganic substances are the activities of the gall bladder mucosa. Certain substances like mucin are secreted to increase the viscosity of the bile. When the gall bladder is isolated by a ligature on the cystic duct, a clear colourless liquid collects in the organ and it is known as white bile because it contains only mucinous material secreted by the walls of the gall bladder.

The gall bladder also reduces the alkalinity of the liver bile and brings about a uniform pressure in the biliary ducts.

Filling and emptying of the gall bladder: This organ exhibits regular contractions, a few times in a minute, as well as long drawn out sustained contractions lasting for several minutes. The pressure inside the gall bladder rises considerably during the contractions.

When the liver secretes bile, pressure in the common bile duct rises to about 50-70 mms of water when bile enters the cystic duct to fill the gall bladder. What exactly induces the gall bladder to expel its contents into the duodenum is not known. Whether the movements of the intestines exert a milking action on the common bile ducts or the gall bladder with its thin muscular wall can force the bile into the intestinal canal, remains to be conclusively proved. The second possibility of an active expulsion of its contents by the gall bladder does seem to occur. This kind of emptying coincides with gastric digestive phase. Evidence from lower animals, favour the active role of the gall bladder. A milking effect on the part of the intestines may not occur except that contraction and relaxation of the gut may close and open, respectively, the sphincter of Oddi. While fats may have an uncertain choleretic effect, they cause to set up contractions of the gall bladder. Proteins do not have this cholagogue action. Acids in the duodenum may bring about emptying of the gall bladder.

Two sets of factors — nervous and hormonal may be responsible for bringing about the periodical emptying of the gall bladder. The reciprocal effects of gall bladder contraction and the relaxation of sphincter of Oddi cannot but be regulated by an integrated nervous mechanism. Psychic influences also play an excitatory role. The effects of sympathetic and parasympathetic nerve stimulation are not clear enough to speak definitely about their respective roles. Probably, even in the human subject, apart from the ever present psychic stimulation, nervous mechanisms are not very important.

Just as in the case of secretin, an acid extract of the duodenal or upper intestinal mucosa was shown by Ivy to induce

contractions of the gall bladder. Cross circulation experiments have confirmed this finding. Ivy has christened the hormonal agent as 'Cholecystokinin' and it is a cholagogue – an agent which by provoking contraction of the gall bladder, brings about expulsion of bile.

GLANDS IN SMALL INTESTINES AND THEIR ROLE IN DIGESTION

It was held till recently that the secretions of the glands in the small intestine, jejunum and ileum, known as crypts of Leiberkuhn, contain enzymes which are very necessary to bring digestion to its final stage to enable the products of digestion to be absorbed. It is the opinion of some workers that food materials need not necessarily be broken into the smallest possible molecules for being absorbed. It was also the teaching for a long time that all the enzymes of succus entericus were released into the lumen of the gut in the manner of pepsin and trypsin which are secretions from merocrine type of glands. The enzymes of succus entericus seem to be contained in the cells of the intestinal epithelium which are shed in large numbers as in the case of holocrine glands. The epithelial cells covering the villi, which possibly are those that contain in their cell matter the various enzymes, are lost into the lumen. Replenishment of the cell population is by gradual migration of the cells from the depths of the crypts of Leiberkuhn. Cells here show active mitosis. The presence of an innumerable finger-like processes, the villi — 1 mm in height and a little less in diameter, gives a velvety appearance to the mucous membrane of the intestines, which also present folds. Surrounding each villus are a few minute dot-like openings of the intestinal glands. The villus is covered by columnar epithelium, having a specialised luminal surface in which are present microvilli, giving a brush border appearance (as in kidney), which is characteristic of surfaces having an absorptive function. The villus has in its core, a layer of plain muscle fibres continuous with the muscularis mucosae. A few lymphatic vessels are also found inside the villus along with a few blood capillaries. The muscle fibres are responsible, by their contraction, for the swaying and pumping movements of the villi. The crypts are tubular glands lined by a layer of

columnar epithelium. Certain other cells occur here and there among the columnar cells—goblet cells secreting mucin, cells that have an affinity for silver stains (argentaffin cells) concerned with synthesis of serotonin and a third variety known as Paneth cells with an acidophil nucleus.

In the duodenum, apart from glands as described above, there are others lying external to the muscularis mucosae (the only such glands in the whole of the alimentary canal. All others are inner to this muscle layer) and these are the Brunner's glands which are comparable to the pyloric glands. These secrete mucous having a protective function in preventing duodenal ulceration as may be caused by gastric acid coming into contact with duodenal mucosa. Fat emulsification may be a subsidiary role, Enterokinase and even the intrinsic factor of Castle may also be components of duodenal juice.

Composition of succus entericus (intestinal secretions): This is more often alkaline in reaction (between 6.3 and 9) than otherwise and the actual constituents vary from one part of the intestine to another. The bicarbonate ion is an invariable component of intestinal juice. It is not possible to estimate the daily output of the succus entericus, in view of the great capacity for absorption in the intestine. Studies of the cellular debris of the intestinal contents have revealed that while enterokinase and amylase may be liberated as a merocrine secretion, the other enzymes are intracellular. It is even held by some workers that the breakdown of disaccharides and short chain polypeptides occurs intracellularly, as these are absorbed through the cytoplasm of the intestinal epithelial cells. Even if it is conceded that digestion takes place in the lumen of the intestine, the release of the enzymes from the epithelial cells must result from the action of trypsin on the cells causing their lysis. Enterokinase is secreted as such and it is not liberated by the destruction of epithelial cells. This makes it certain that the activation of trypsinogen by enterokinase will always be independent of any process bringing about the disintegration of the epithelial cells.

Quite a number of enzymes are present in the succus entericus. The more important ones are — an aminopeptidase, tri—

and di-peptidases, a lipase, disaccharidases (maltase, sucrase and lactase) and enterokinase.

Proteolytic enzymes — The aminopeptidase splits off the end amino acids having a free amino group and hence is to be considered an exopeptidase. The tri- and di-peptidases break up tri-peptides and di-peptides respectively, into amino acids.

Intestinal lipase is a weak, fat hydrolysing enzyme. The disaccharidases cause the breakdown of the respective disaccharides into constituent monosaccharides.

	Sucrase	
Sucrose	----->	Glucose + Fructose.
	Maltase	
Maltose	----->	Glucose + Glucose.
	Lactase	
Lactose	----->	Glucose + Galactose.

The action of enterokinase has been described in relation to trypsin, the pancreatic enzyme.

Control of secretion of intestinal glands: The Brunner's glands appear to be under nervous (parasympathetics — vagus is excitatory), as well as hormonal control. The latter is demonstrated by the fact of secretion in a denervated duodenal pouch. A specific hormone, duocrinin which is present in crude secretin preparations, is thought to be involved in evoking duodenal secretion. Pure secretin does not have any action in this regard.

Techniques of study of intestinal functions — just like the Pavlov's pouch, a short length of the intestine from any part of it is isolated by sectioning it at two points. One end of the segment is closed and the other brought out through a wound in the abdominal wall, so that secretions accumulating in it could be collected from outside. The continuity of the intestine interrupted by the removal of a small length is restored by joining the divided portions end to end. This preparation is known as Thiry loop, which is an innervated though isolated portion of the intestine. A modification of the Thiry loop is the Thiry-

Vella loop in which both ends are open and brought out through the abdominal wall to form a double fistula. This second type of preparation retains its nervous and vascular connections with the rest of the intestines. Ivy transplanted a Thiry loop near the mammary gland of a lactating animal, a technique he used also in the case of the stomach. The intestinal loop has neither nervous nor vascular connections with the intestine. It can respond only to hormonal factors carried by blood from the alimentary canal.

In man, intestinal secretions can be collected by passing a Miller-Abbott tube which has actually three concentric compartments throughout its length. The innermost and the outermost can be inflated with air to render the tube incompressible and to maintain the patency of the intermediate compartment which has openings leading to the outside of the tube and when the end of the tube is in the intestines, its contents could be aspirated through the openings into the intermediate compartment. It must be borne in mind that mechanical stimulation of the mucous membrane, as by the passage of the Miller-Abbott tube itself and by distension of the intestine, caused by the inflation of the tube, is sufficient to evoke profuse secretion of intestinal juice. The Thiry loop and its modifications preclude mechanical stimulation to a large extent, though even the introduction of a cannula into the loop itself will bring forth a larger volume of juice than is normally secreted by the glands.

The role of nervous mechanisms in controlling the secretion of intestinal glands has yet to be conclusively demonstrated. Sectioning the sympathetic fibres increased secretory activity and this is called paralytic secretion. This activity is augmented by stimulation of the vagus or administration of parasympathomimetic agents like eserine. It is abolished or diminished by atropine. The effects of cutting sympathetic fibres may be due to the resulting vasodilatation or increased motility of the intestines. This latter effect may bring about mechanical stimulation of the intestinal glands.

While mechanical stimulation of the intestinal wall is important, chemical factors as present in the chyme, are equally

so. Extracts of intestinal mucosa (after it has been in contact with chyme from the stomach) from which secretin and vasodilator substances have been removed, when injected intravenously, brought about increased secretory activity of the intestinal glands in an isolated intestinal loop. The active principle involved in this mechanism has been termed enterocrinin, which causes an increase in the volume of succus entericus. Whether there is another substance like pancreozymin concerned with raising the enzyme content, is not satisfactorily shown. It may be that the parasympathetic nerves to the intestinal gland may have some role in this regard.

The crypts of Leiberkuhn, in addition to providing enzymes for bringing about the final digestive changes before absorption of the products of digestion, contribute water to help dissolve the solids of the intestinal contents as well as for emulsification of fat.

Large intestine (Colon): While the epithelium in this part of the alimentary canal forms glands, there are no villi as in the small bowel. Goblet cells are more numerous. Enzymes are secreted but in diminishing quantity as the colon is traced downwards. The secretions of the glands form an alkaline watery fluid with mucus. The colonic glands respond to irritation by any agent, by secreting mucus in large amounts.

The nervous regulation of colonic secretion is by the parasympathetic fibres of vagus to most of the colon and the nervus erigens, to the terminal part. Sympathetic excitation reduces the response to vagal stimulation or that of the nervus erigens.

The intestines may have a minor role as an excretory organ. Even in prolonged states of starvation, fat is present in the stool. It therefore follows that it is excreted from the intestinal wall. The ability of the large intestine to excrete substances, is made use of in the therapeutic innovation known as colonic lavage. A tube with a double lumen and made of rubber, is passed into the upper reaches of the colon and water is allowed to flow through the tube and the colon. The water carries away with it certain diffusible constituents of blood. When there is kidney failure, the blood urea can be brought down by means of colonic intuba-

tion. Since other constituents of blood may also be washed away, they are added to the fluid perfusing the large intestine. The physiological role of the colon is to absorb the water and salts and reduce the volume of the intestinal contents gradually and also to alter the consistency of the faeces from a fluid condition to that of a semisolid.

A line is necessary to sum up the role of the various gastrointestinal hormones. Most of these (secretin, pancreaticozym, cholecystokinin, duocrinin), excepting gastrin and possibly villikin and enterocrinin, are elaborated by the mucosa of the duodenal region and so the duodenum has been fancifully called the hypophysis of the alimentary canal. Each of these hormones promotes the secretion of the appropriate alimentary juices or brings about movements or contractions of the plain musculature of some part of the digestive canal.

ABSORPTION OF PRODUCTS OF DIGESTION

While drugs may be absorbed from mouth, food stuffs are minimally absorbed at the earliest instance, in the stomach whose wall is not adapted for such a function. Glucose is probably the only digestive product taken up by the wall of the stomach. Alcohol is absorbed in appreciable amounts and so also iron.

The mucous membrane of the small intestines is especially suited for an absorptive function — the presence of a large number of microvilli on the luminal surface of intestinal epithelial cells increasing the surface area of the cell, is the evidence for such a function.

Absorption of substances can be studied by means of the Thiry or Thiry Vella fistula. Substances that can be identified by tagging them with radio-active isotopes have helped in elucidating the mechanism of absorption. In man, the use of the Miller-Abbott's tube has advanced the knowledge regarding the modes of absorption, especially when combined with tracer techniques employing radio-active isotopes. Certain non-absorbable materials called 'markers' (like phenol red) are mixed with substances whose absorption is intended to be studied. The concentration

of any substance that is being absorbed is estimated with reference to the strength in which the marker remains after absorption. Absorption has been studied in isolated loops of intestine removed from the body (experimental animals) and preventing the contents in the loops from getting mixed with the fluid in the bath in which a loop is suspended. The 'everted sac' method in which the intestines are turned inside out, so that the absorbed materials collect in the inside of the everted loop, is available for study. This is a method complementary to the others described above. The influence of variation of temperature, drugs and other factors on absorption, can be revealed by the various techniques, especially those in which isolated loops from experimental animals are utilised.

From studies using heavy water (Dueterium oxide), it has been concluded that water is definitely absorbed in the stomach, though at a slow rate. The absorption is very much more in the intestines in which hydrostatic and osmotic pressures have an influence on the rate of absorption. In the large intestine, hydrostatic pressure is important in facilitating absorption of water. High osmotic pressure of the intestinal contents hindered water absorption. Inorganic salts are absorbed in company with water. The tonicity of the mixture of water and salts absorbed will depend inversely on that of the intestinal contents. Presence of potassium and calcium in the intestinal contents seems to increase the absorption of water and chloride. Atropine increases the salt and water absorption, inhibiting secretion of the intestinal glands. The absorption of water and salts is, in the main, an active process, though concentration of salts in the lumen of gut has an influence on this.

Carbohydrates:— Almost all of the carbohydrate in the food is absorbed in the form of monosaccharides. The intestines can absorb monosaccharides much more easily than disaccharides, while polysaccharides are not at all absorbed. Hexoses are preferred to pentoses. Galactose is absorbed at a higher rate than glucose and fructose least of the three. Absorption can occur against a concentration gradient. There is a carrier mechanism underlying this absorption and while at very low concentrations of glucose, the rate of absorption rises with strength of the solu-

tion, yet at a strength of 5%, the carrier mechanism is saturated and no rise in rate occurs. The absorption rate is greater in the higher reaches of the small intestine and progressively falls towards the terminal portions. Glucocorticoids and thyroxine promote the absorption of glucose. A certain concentration of salt (potassium and sodium) seems to be necessary for enabling the intestines to absorb glucose. Pentoses are not actively absorbed. It appears that sucrose, maltose and lactose are hydrolysed in the cells absorbing them.

Proteins :— Amino acids arising out of protein digestion are easily absorbed and even among these, some are taken up at a more rapid rate than others. While glycine and alanine are at the head of the scale, leucine and valine are the least preferred. Basic amino acids move more slowly across the cells than neutral ones. This shows that chemical structure has some importance in this respect. Laevo isomers (naturally occurring ones) are definitely preferred to dextro forms. The former are transferred by an active transport, while the latter are absorbed passively. Metabolic inhibitors and anoxia interfere with those absorptive mechanisms which seem to be shared by hexoses. The absorption of a sugar is hampered by the presence of amino acids. The intestinal epithelium can pick and choose amino acids and hence alter the composition of the mixture of amino acids presented to it. Transamination of aspartic and glutamic acids may occur in the intestinal epithelium, as they are absorbed. Short length polypeptides may be taken up by the intestinal mucosa but before they are transferred to the blood stream they are hydrolysed to amino acids. The ability to absorb protein as such may exist in the new born of many mammals. Antibodies from the mother's milk can enter the blood from the gut so as to confer immunity on the young animal. This faculty is lost with the passage of time. Allergic states may originate from absorption as such of native protein, whose presence in the plasma can be demonstrated by immunological methods. Such absorption may occur in a normal intestine or in inflammatory conditions.

Fat absorption :— This is a matter of some controversy. Bile salts which are responsible for emulsification of fats have been thought to aid in the absorption of fat in small droplets or

chylomicrons. Doubts have been raised about the importance of emulsification in being directly responsible for rapid absorption. Pancreatomy resulted in the absence of lipase in the intestinal contents. It was observed that absorption of fats was consequently hindered.

Two views were held till recently. According to Pfluger and Verzar (lipolytic theory), neutral fats were broken down completely by lipase to glycerol and fatty acids, emulsification by bile preceding the hydrolysis. Since fatty acids are insoluble in water at the pH obtaining either in duodenum or farther down, they are rendered soluble by forming complexes with bile salts and it is in this form that fatty acids are absorbed. During the passage through the intestinal epithelium, neutral fat is reconstituted and absorbed as such into the lacteals. The bile salt is detached and set free into the gut for recycling. Phosphorylation of the glycerol is necessary for the resynthesis of neutral fat.

Frazer (partition theory) opined that complete hydrolysis of neutral fat is not necessary for absorption. Partial breakdown of some amount of fat by lipase to form monoglycerides and diglycerides is sufficient to bring about thorough emulsification of the rest of the unconverted neutral fat, in the presence of bile salts. The emulsified fat contains very small fat globules (0.5 in diameter), which are individually covered by a layer of lipoprotein (to maintain the state of emulsification) and these are absorbed into lacteals. A small amount of fatty acid which may be released by fat hydrolysis is absorbed after forming complexes with bile salts, as postulated in the rival view.

The latest concept is that, about a fifth part or more of the entire neutral fat in the gut is broken down to glycerol and fatty acids, as revealed from isotope studies. The rest of the fat is converted to monoglycerides. Both the fatty acids and the monoglycerides form very minute particles, called micelles, in combination with bile salts and it is in this form that they are absorbed by pinocytosis. In the course of hydrolysis of fats in the gut, triglycerides may be reformed in a new combination, (different from that of the fat ingested) both in the lumen and in the epi-

thelial cell of the intestinal lining. Short chain fatty acids, however, are absorbed as they are, into portal blood and are carried away to the liver. It is only the long chain ones that are used to resynthesise neutral fat. It has been suggested that a complicated chain of reactions involving several enzymes, takes place in reconstituting triglycerides, step by step from fatty acids through the stages of mono and diglycerides. The neutral fats are transported through the lymph channels as chylomicrons with a protein covering. The absorption of fatty acids can go on against a concentration gradient and this process seems to need oxygen.

While in the dog, fat absorption takes place in the distal parts of the small intestine, in man it occurs in the proximal lengths of duodenum and jejunum. Adrenal cortical hormones are required, in some unknown manner, for the absorption of fats. Probably, these hormones are necessary to maintain the proper ionic balance for fat absorption or for fat resynthesis.

Vitamins : Water soluble vitamins (B complex and vitamin C) are absorbed without any hindrance. Fat soluble vitamins are taken up from the gut in a manner similar to fat. Bile salts are necessary for this. When the bile duct is obstructed and jaundice is caused thereby, Vitamin K is not absorbed and a tendency to bleeding may be seen. Vitamin A which is in the form of a complex of Vitamin A and fatty acids, is absorbed just like neutral fats. Free Vitamin A does not need bile salt for its absorption, while carotene requires it. Mineral oils interfere with vitamin absorption.

MOVEMENTS OF THE ALIMENTARY CANAL

The movements of the alimentary canal are mainly intended to propel its contents from one part to another in the aboral (away from the mouth) direction. In addition, the rendering of food eaten, into a suitable consistency by mastication (chewing), for the action of the digestive juices, the thorough mixing of food and gastric and intestinal secretions caused by the churning movements of the stomach and the segmenting movements of the small bowel and the absorption of the products of digestion

brought about by the swaying and pumping actions of the villi, are other purposes which are achieved by these movements.

Chewing or mastication: The teeth, the molars and the premolars, grind (masticate) the food placed in the mouth, into a paste-like consistency. The incisors and the canines, especially in the carnivorous animals, are used to bite off portions or tear large chunks of meat into smaller pieces before taking it into the mouth. The molars are of great importance in the cud-chewing (ruminant) animals. Mastication is due to the side to side and vertical movements of the lower jaw in relation to the immovable upper jaw. These movements, when coordinated, make the jaw appear to perform a rotational manoeuvre. The masseters, the temporal muscles and the two pterygoid muscles. (medial and lateral), all innervated by the 5th cranial nerve, are the main muscles involved in the chewing action. The buccinators which also assist, are supplied by the facial (VII) nerve. The forward movement of the jaw is accomplished by the pterygoid muscles. The backward movement is effected by the temporal and geniohyoid muscles. The temporal muscles, the masseters and the internal pterygoids bring about closure of the mouth by elevating the lower jaw. The opening of the mouth is brought about by the digastric and mylohyoid muscles. The grinding action occurs when the lower jaw slides past the upper one, making the lower molars move forward (pterygoid action). The paste-like mass resulting from the action of chewing is shaped into an ovoid form (bolus) and is covered with saliva and made suitable for swallowing.

It is a moot point, if chewing is necessary as a preliminary to the action of the digestive enzymes. In the conscious subject, mastication is a voluntary act. It can be elicited by the stimulation of certain areas in the cerebral cortex, as well as being reflexly evoked by stimulation of the mouth. A medullary centre is also thought to be present and it may coordinate the various movements comprising mastication.

Swallowing: This process also known as deglutition is responsible for moving the bolus from the mouth, past the

pillars of fauces, through the oropharynx and the oesophagus into the stomach. Magendie described this as occurring in three stages which are now referred to as the oral, the pharyngeal and the oesophageal stages (formerly the I, II and the III stages respectively).

I or oral stage: This can be brought about voluntarily. The bolus (see above) comes to lie on the upper surface of the back part of the tongue which is lifted up and drawn backwards by the action of myelohyoids, and made to approach the hard palate by the contraction of hyoglossi, glossopalatini and styloglossi. Respiration is temporarily arrested and this state continues till the end of the next or second stage. The bolus is as it were, shot into the pharynx.

II or Pharyngeal stage: In the human subject, the coming into contact of the food material with the posterior pharyngeal wall, the pillars of fauces, the soft palate and the posterior part of the tongue (any one of these will do), sets up the swallowing reflex which goes out of voluntary control from now on. The further progress of the bolus can possibly be into any one of four passages but three of these are closed to the bolus. The entry into the nasopharynx is barred by the elevation of the soft palate (which is made to touch the posterior wall of the pharynx), caused by levator palatini and tensor veli palatini. The vocal chords are adducted, closing the glottis and the larynx is displaced anteriorly and upward, so as to lie under the epiglottis, past which the bolus is thrown back at the posterior pharyngeal wall. The inhibition of respiration is maintained. The re-entry into the mouth is prevented by the elevation of the tongue with resulting positive pressure above it, as well as the narrowing of the isthmus of the fauces brought about by the contraction of pharyngopalatini and glossopalatini muscles. The superior pharyngeal constrictor muscle contracts and starts off the rapid downward movement of the food material. The upper oesophageal opening which was closed tonically (cricopharyngeus action) dilates and receives the bolus.

The III Stage: On the arrival of the food at the upper end of the oesophagus which is relaxed to receive it, a downward

peristaltic movement of the oesophagus seizes the bolus and carries it towards the stomach. The swallowing act is in no way hindered even in the upside down position of the subject. Gravity plays no great role except in assisting the progress of the bolus downwards. Muscular movements are primarily responsible for the oesophageal stage also. In the case of a fluid, gravity does help to squirt it down.

The vagus is excitatory to the oesophageal musculature which is partly of the striated type (upper portion) and the rest, plain muscle.

The lower end of the oesophagus serves as a sphincter (cardiac sphincter) which relaxes when the vagus is stimulated. Normally, in the absence of swallowing movements, it is constricted, preventing the entry of gastric contents into the oesophagus. Dilatation occurs when the peristaltic wave, sweeping the bolus with it, arrives at the lower end of the oesophagus and after the food passes into the stomach, this part of the oesophagus once again contracts, narrowing the opening. When a swallowed liquid pours down the oesophagus, it accumulates above the cardiac sphincter which opens only when the peristaltic wave set up by the swallowed fluid, at the upper end of the oesophagus, reaches it. Consequently, strictures occur, as a result of swallowing corrosive fluids and these are seen in the upper and the cardiac ends of the oesophagus.

The first and second stages are over within a second each, while the third stage occupies about 6 seconds in the case of solids, the delay in the lowest part of the oesophagus being as much at 3 sec.

Nerve centre for deglutition: A diffuse collection of neurones in the floor of the IV ventricle of the medulla, lying close to but in distinct from the respiratory centre, coordinates the activity of the several striped and plain muscles taking part in the act of swallowing, so that the orderly contraction and relaxation, in the proper sequence, can occur.

The different mechanisms comprising the deglutition process have been studied by means of X-ray cinematography while a

subject swallows a radio opaque fluid containing barium sulphate.

Dysphagia or difficulty in swallowing is a symptom of growths of the oesophagus, oesophageal strictures usually caused by drinking corrosive fluids and sometimes of paralysis of the nervous mechanisms. Achalasia is the inability to relax of the lower oesophageal 'sphincter' in response to the arrival of a peristaltic wave. Heartburn is the painful sensation felt behind the sternum, in the midline, caused by the irritation of the oesophageal mucosa when gastric acid is regurgitated into it. During a meal, a small quantity of air is swallowed along with each mouthful of food. This accumulates in the lowest part of the oesophagus and is expelled all at once, giving a sense of relief. This phenomenon is known as belching.

Stomach movements: The stomach is the widest part of the alimentary canal, as well as the most developed, as far as musculature is concerned. On this account, its walls are thicker than those of any other part of the digestive tract. It has three layers of muscle – the outer longitudinal, running roughly from the cardiac towards the pyloric regions, the middle circular fibres and the innermost oblique fibres starting from the oesophageal region and coursing downwards on either side of the lesser curvature (see below) and diverging away from it. They merge ultimately with the circular fibres. The muscularis mucosae is very well developed and is probably concerned with the emptying of the gastric glands.

The shape of the stomach varies depending on the degree of tone of its muscle fibres. The most common form is that of the J-shaped stomach and the others being the reversed L-type and the steer horn stomach (musculature exhibits excessive tone). Viewed from the anterior aspect of the body, the stomach has two borders, the lesser curvature on the right and the greater curvature on the left, both completely outlining the shape of stomach. The entire stomach is divided into four conventionally recognised regions (From the point of view of movements & not histologically)-cardiac end, fundus-the portion above a horizontal plane

passing through the cardiac part, the body of the stomach and the pyloric part. (Fig 20). The pylorus is separated from the body by a notch on the lesser curvature—the *incisura angularis*. There is a notch not so marked, on the greater curvature, opposite the *incisura*. The term pylorus should refer to the pyloric antrum, the wider part distal to the *incisura angularis* which is continuous with the narrower pyloric canal, with the pyloric sphincter around the latter. The antrum and the canal are separated by the *sulcus intermedius*, if present. The first two inches of the duodenum is called the duodenal cap. Functionally, the antrum, the sphincter and the duodenum act as a single unit.

At the oesophago-gastric junction, there is no anatomically marked sphincter, but functionally this region behaves like a sphincter controlling the entry of food into the stomach. On the other hand, the pyloric sphincter while appearing to be an anatomical entity, does not regulate the emptying of the stomach. The pylorus seems to prevent regurgitation of intestinal contents into the stomach as well as to limit the amount of stomach contents expelled into the duodenum. Surgical resection of the pyloric canal does not interfere with normal emptying of the stomach. The mucous membrane of the pyloric canal is thrown into folds by the *muscularis mucosae* whose fibres run in a radial direction. These folds may have a valve-like action in preventing regurgitation.

The vagus innervates the gastric muscle. The effects of vagal stimulation depend on the condition of the stomach wall prior to vagal stimulation. Thus, if the tone is already high, relaxation will occur. But contraction will be seen if previously existing tone is low. Vagotomy, as was practised in the treatment of peptic ulcer causes profound disturbances in the gastric function. The tone and motility are very much lowered and so emptying of stomach is very prolonged.

The stomach was said to exhibit two different kinds of activity – hunger movements and digestive peristalsis. It is now felt that this kind of division does not give a true picture. The two kinds of movements are but two different aspects of the same underlying activity. The different names only refer to the state of emptiness or being filled, of the stomach.

Hunger contractions: Carlson described three types of activity when the stomach was empty. In type (1), weak contractions of the entire stomach appear thrice in a minute, the resting phase in between contractions lasting 3 or 4 seconds. Type (1) may give place to type (2) in which the intragastric pressures rise much higher (upto 100 cms. of water). The time course is about the same as in the previous type. Type (3) activity is rarely seen in the human stomach. It consists of a kind of partial tetanus in which the basic tone is higher than in the other two cases, type (2) activity being superimposed on this raised basal tone. Hunger contractions (tonus rhythm) come on immediately after the stomach has emptied itself completely. As time goes on, these contractions become more vigorous, occurring for about half an hour, after which a quiet interval of 2 to 3 hours may ensue. Again hunger contractions may come on and this may be followed by a period of quiescence. The contractions when severe, coincide with a sensation of hunger. When very severe, the contractions produce pain and these are known as pangs of hunger.

Hunger contractions can be recorded by introducing a balloon of suitable size connected by flexible rubber tube to a water manometer carrying a float with a stiff wire with a writing point on it. The balloon is inflated. The contractions of the stomach cause pressure changes in the stomach which are transmitted to the air in the balloon which, being in communication with the manometer, cause the writing point to move up and down and thereby to permanently record the gastric movements on a rotating drum with a smoked paper on it.

When food enters the stomach, hunger contractions cease immediately. As more and more food enters the stomach, it relaxes to accomodate the newly arrived food. Thus the, intragastric pressure is prevented from rising. This phenomenon is known as the receptive relaxation of the stomach which is a reflex effect. After a little while, peristaltic contractions (digestive peristalsis) start appearing in the body of the stomach and run down the organ towards the pylorus. Some peristaltic waves end at the incisura angularis, others at the pyloric canal, in which case some of the contents may be expelled into the duodenum.

The contraction of the pyloric canal which occurs at the end of the peristaltic wave may either push the acid chyme into the duodenum or back into the body of the stomach (churning movement). These movements have been studied by viewing the shadow (thrown by X-rays on a fluoroscopic screen) of the stomach after a barium meal. Each peristaltic wave takes about a minute to travel from the point of origin to its termination in the pylorus. Since the frequency is about 3 per minute, there can be 3 waves travelling down the stomach at any time. The contraction of the pylorus is brought about by its distension caused by the pushing of gastric contents, by the peristaltic wave into the canal. When the peristalsis approaches the pylorus, the duodenal cap relaxes in anticipation. When the pylorus contracts, the duodenal cap also contracts simultaneously, propelling gastric contents into the intestinal canal thereby preventing regurgitation of duodenal contents into the stomach.

Cole compared the peristaltic activity of the stomach to a cycle of systole and diastole. When peristalsis was weak, he called the phase as one of diastole and when it was strong, he termed it as systole.

Gastric filling: Studies were made in animals by feeding them with several portions of food, each coloured differently by dyes. These animals were killed immediately after feeding them and the stomach with its contents was quickly frozen and sectioned. From the study of the sections, it was learnt that the earliest portions occupied the most dependent part of the stomach cavity, to be in contact with the greater curvature and the subsequent mouthfuls piled themselves up in a regular manner so that the last portions came to lie against the lesser curvature. In the case of liquids like water, as soon as they entered the empty stomach, they ran down the furrow in the mucous membrane on the inner aspect of the lesser curvature (Magenstrasse) and were immediately expelled into the duodenum. But when liquids were swallowed, especially in large amounts, with solid food in the stomach, the fluid spread between the food mass and the stomach wall.

Emptying of the stomach: It appears that most of the gastric peristaltic activity is meant to churn the food to ensure

thorough mixing of the gastric juice and the food substances. In this respect, the pylorus resembles the gizzard of the bird stomach which crushes large solid masses into finer consistency. The churning movements bring about the formation of acid chyme which is a paste-like and semisolid mass and acidic in reaction. Several factors seem to influence the rate at which the stomach empties itself of its contents. It has been observed that the quantity expelled from the stomach is a constant fraction of its contents and this is under the influence of several factors like consistency of food, pH, chemical nature and osmolarity. Solids are delayed in the stomach till they are ground to a semi fluid or fluid consistency. This is achieved by the churning movements (see above). Liquids like water leave the stomach very rapidly. Other liquids will take more time, depending on their chemical properties. Acids of very low pH take longer to leave the stomach. The purpose in delaying acids is to bring about their neutralisation to a more acceptable pH, in the intestinal canal. Such slow emptying in the case of acids, serves to protect the duodenal mucosa from excess acidity. Highly concentrated solutions (hypertonic) as well as weak solutions of sugar and electrolytes are hindered in their onward passage till the fluid becomes approximately isotonic. In the case of hypertonic solutions, water may be added by the stomach wall and as regards weak solutions, water may be absorbed by the stomach wall.

Fats take longer to leave the stomach. Proteins require less time and carbohydrates the least.

There are two mechanisms which seem to control the emptying of stomach. The entry of highly acidic solutions into the duodenum sets up a reflex mediated through the vagus — the enterogastric reflex — the effect of which is to inhibit gastric peristalsis. The presence of food materials like fats and fatty acids in the duodenum causes the release of a hormonal factor known as enterogastrone (see under digestive aspects of gastric function), which inhibits the motility of the stomach. It is an everyday experience that highly fatty foods are very satisfying from the hunger point of view and they increase the intervals between food intake by suppressing hunger contractions. Products of protein digestion like proteoses and peptones are also responsible

for bringing about the enterogastric reflex, while sugars not only act reflexly but also through the hormonal factor. Gastric evacuation starts as soon as even part of its contents is rendered suitable to be expelled, chemically and physically and it occurs once in about 20 seconds in man and continues till the stomach is emptied out.

Thin gruel (liquid) leaves the stomach completely in about $2\frac{1}{2}$ hours, while a standard barium meal (semi-solid) takes about 6 hours to leave the stomach without a trace. While excitement, anxiety and resentment accelerate emptying of the stomach, fear and anger delay it. These facts were first noted by the American Physician, Beaumont in the French Canadian, Alexis St. Martin, who had a gastric fistula caused by a gunshot wound of the abdomen.

Vomiting: The ejection of gastric contents and very rarely those of the small and large bowel, through the relaxed cardiac orifice and oesophagus and by way of the mouth, is known as vomiting. This requires a co-ordinated action of the muscles of the stomach, oesophagus and abdominal wall. This is really a reflex caused by mechanical irritation or chemical irritants in any part of the alimentary canal. The afferent fibres are present in vagus and sympathetic nerves. Some of the substances provoking vomiting, act as follows:

Tartar emetic stimulates vagal afferents. Mercuric chloride excites sympathetic fibres. Mustard, copper sulphate and zinc sulphate affect both systems of fibres. Disagreeable sights, nauseating odours and such other non-alimentary stimuli can also provoke vomiting. Such an effect is known as psychic vomiting. Excitation of the vestibular apparatus, as by travelling in a bus or train or a ship (sea sickness), can also bring about vomiting. Certain drugs like apomorphine and picrotoxin can bring about vomiting by acting directly on the vomiting centre, said to lie near the respiratory centre but separate from it. These agents are called central emetics. The occurrence of vomiting (during pregnancy), either of mild degree (morning sickness) or of severe extent (hyperemesis gravidarum or pernicious vomiting)

seems to be due to a heightened irritability of the vomiting centre caused by carbohydrate deprivation. In certain neurological conditions, projectile vomiting may occur without attendant nausea.

The condition of nausea is experienced as a preliminary to vomiting. Profuse salivation occurs during nausea. Due to the relaxation of the pylorus, material from the proximal portions of small bowel enters the relaxed stomach. During actual vomiting, deep peristaltic contractions originate in the middle of the stomach and these reach the incisura where a tight ring is formed. A brisk contraction of the diaphragm and the abdominal muscles raise the intra abdominal pressure which exerts its effect on the relaxed upper part of the stomach. The cardiac orifice and the oesophagus are completely relaxed. Respiration is arrested, the glottis is closed, and the gastric contents are expelled from the stomach to be thrown out through the mouth. Retching includes the contractions of the various muscles, and is indicative of efforts preliminary to actual vomiting. Antiperistalsis is not usually seen though churning movements may occur.

It is significant that the vomiting centre is situated close to the tractus solitarius, the respiratory centre, the swallowing, defaecation, vasomotor and vestibular centres in the medulla. The multiplicity of stimuli, any one of which can bring about vomiting, is suggested by this anatomical fact. Cardiac relaxation is very important in vomiting. The cardiac sphincter is tonically contracted in coughing and defaecation. Otherwise, gastric contents will be expelled and vomiting may occur.

In infants, vomiting is by antiperistalsis in the stomach. When a large feed is given to a baby, the excess is regurgitated in this manner.

Very rarely, faecal material may be thrown out in vomiting, as in intestinal obstruction, in late stages.

Intestinal movements: The wall of the small intestine has in its muscle or middle layer, two kinds of plain muscle fibres. Of these, the external one is that of the longitudinal fibres running

along the direction of the intestines themselves. The inner one is formed by circular muscle fibres and this is considerably thicker. It is mainly responsible for the movements of the intestines. While the longitudinal fibres should also be involved in intestinal movements, their exact contribution is not clearly understood. Between the two layers of muscle fibres is situated, the myenteric or Auerbach's plexus. The Meissner's plexus is just external to the mucous membrane. The two plexuses are interconnected by nerve fibres. The Auerbach's plexus has many nerve cells in it. The vagus and the sympathetic nerves terminate in the Auerbach's plexus, their fibres intermingling. The preganglionic parasympathetic fibres of the Vagus end in the Auerbach's plexus from which fresh fibres arise and innervate the plain muscle as well as the glands in the mucous membrane and the muscularis mucosae through the Meissner's plexus. The sympathetic postganglionic fibres are derived from the superior mesenteric plexus but pass directly to the effector cells.

While in the former days, three kinds of movements were described—viz—1) segmenting movements, 2) Pendular movements, 3) peristalsis, —now it is certain that of the three, pendular movements are nothing but segmenting movements and the reason for considering them as a separate kind of movement was a misunderstanding of Ludwig's term, pendular movement, by which he really meant a rhythmic movement but not contractions of the intestines travelling up and down.

Segmenting movements: These have been studied by means of X-rays after giving a barium meal. The small intestine was divided into numerous segments by the formation of rings of constriction. A little later, new segments were formed by the development of constriction rings in former segments and the adjoining halves of neighbouring segments fusing together, the older ring of constriction having relaxed. This movement helps to mix the intestinal contents as well as to promote absorption. Two kinds of segmenting movements have been described, one is the eccentric type in which there is no complete ring of constriction entirely surrounding the intestine, but only part of the wall shows constriction. In the other type there is a complete ring of constriction (concentric type). The ring is formed by contraction

of more than 2 cms. of intestine. The rate of segmental movements seems to diminish progressively towards the end of ileum, the duodenum exhibiting the highest rate. Segmenting movements seem to be mainly due to an inherent myogenic activity, though nervous influences may also play a role. Segmenting movement is also susceptible to the action of drugs.

Peristalsis: When the small intestine is stimulated at any point along its length, contraction of the musculature occurs, both proximal and distal to the point of stimulation. These contractions, spread in the oral and aboral directions. In the former case they come to an end very soon, while the downward or aboral spread continues to cover a considerable length of the small intestine and to this latter type of spread of contraction, the term peristalsis is given. Peristalsis does not mean a progress of the contraction along a fully relaxed intestine. It is superimposed upon the segmenting movement which can occur simultaneously. The main purpose of peristalsis is to push or sweep the intestinal contents towards the colon (large intestine). The rate of the progress of a peristaltic wave, if it can be so called, is about 1 – 2 cms per minute. This is responsible for moving the contents over short stretches of intestine. Less commonly and in between long intervals, a peristaltic wave may travel down covering very long stretches at rates upto 25 cms per sec (2–25 cms, average 10 cms) may be seen. This type of movement is referred to as peristaltic rush and this is responsible for shifting the contents of the small bowel over much longer lengths. Cathartics (purgatives) set up the peristaltic rush, the time taken for completing the entire movement from pylorus to the rectum being less than a minute.

It is possible that the stimuli which set up segmenting movements or peristalsis may differ only in intensity. The state of excitability of the bowel may also be a factor in determining whether segmenting movements or peristalsis should be evoked in response to a stimulus.

In view of the spread of a peristaltic movement along the intestine, it is reasonable and logical to think of a nervous basis for this activity. Bayliss and Starling propounded the law of the

intestine, according to which if any point in the intestine be stimulated there is contraction of the muscle immediately proximal to it and relaxation of the wall of the intestinal portion distal to the point of stimulation. They were of the opinion that the presence of a mass of intestinal contents anywhere in the bowel provoked a contraction proximal to it but a relaxation beyond it and this made the mass move downwards. The setting up of a peristaltic wave by the stimulation of the wall of the intestine, was termed the myenteric reflex, by Cannon. Drugs like nicotine abolish this reflex.

Alvarez suggested that the properties of the intestine, like excitability, rhythmicity and conductivity of the small intestine, show a progressive decrease in the aboral direction. This, according to him, was responsible for the existence of a downward gradient along the length of the bowel, which was responsible for the aboral progress of the peristaltic wave. It appears that there is some kind of metabolic gradient, as in the case of the heart, from the pacemaker to the farthest reaches of the cardiac muscle. More about this will have to be elucidated.

The intestinal villi: These are small finger-like projections, seen in the mucous membrane of the intestinal wall which itself is thrown into circular folds to increase the absorptive surface. A villus is about a millimetre in length. At its core, there is a filament or two of plain muscle. An inactive villus lies on the surface of the mucous membrane but, in the presence of products of digestion and water in the lumen of the gut, it exhibits a swaying or lashing motion as well as a shortening and lengthening movement. Though doubted by some, this motor activity is most probably responsible for promoting absorption. The activity of the villus is increased by sympathetic nerve stimulation (splanchnic nerve) and by drugs like noradrenaline. Villikin, a hormone released from the duodenal mucosa seems to promote these movements.

The ileocaecal valve: The oblique direction in which the last portion of the ileum joins the caecum causes the formation of a valve-like structure of the ileocaecal orifice, which is seen as a slit-like opening on a papilla-like elevation, with the walls of the caecum forming two lip-like structures (Upper and lower) by

invagination of the colon by the ileum. The two lips fuse at their ends giving rise to folds one at each end and these are continued all round the wall on the inside of the colon by a fold. When there is distension of the caecum, there is tension on the fold in the colonic wall which stretches the lips of the ileocaecal orifice, thereby preventing re-entry of caecal contents with high bacterial populations, into the more or less sterile ileum. On the other hand, ileal contents are periodically emptied in small jets into the caecum. It is taken for granted that it is not the circular muscle fibres that surround the ileocaecal opening, that prevent the regurgitation of caecal contents but the valve-like structure of the opening that is actually responsible.

In emotional states or after swallowing food, the contents of ileum are ejected more frequently. The latter mechanism is known as gastro-ileac reflex. The purpose of the ileocaecal valve is to prevent premature expulsion of ileal contents into the caecum as well as to avoid re-entry of matter which has a high bacterial content, into the ileum.

Large intestinal movements: A special feature of the structure of the colonic wall, is the presence of three bands of longitudinal muscle fibres (the taenia coli) running over the entire length of the colon upto and including the sigmoid colon in which however, the taenia tend to spread out or scatter. In the rectum, the longitudinal fibres encircle it entirely, though anteriorly and posteriorly, bands can still be recognised. Since the taenia have a shorter length than the colon, the colon is puckered into pouches and sacculations which are called haustrations. The vagus supplies motor fibres to part of the colon upto the first half or third of the transverse colon. The rest is innervated through the pelvic nerves (nervus erigentis) from the 2nd, 3rd and 4th sacral nerves which are cholinergic. Sympathetic inhibitor fibres arise in the lumbar segments and pass through the inferior mesenteric plexuses to end in the proximal portions of the colon. Fibres from the 2nd and 3rd lumbar segments pass to the inferior mesenteric ganglion and thence to the distal colon through lumbocolonic nerves and presacral or hypogastric nerve. The post ganglionic fibres pass through the pelvic plexus. Stimulation of lumbocolonic nerves brings about relaxation of distal colon.

The ileocolic, the internal and the external sphincters, have reciprocal innervation. In the case of ileocolic sphincter, sympathetic fibres are motor in action. Vagus has no effect on this sphincter. The pelvic nerve is inhibitory to the internal sphincter while the sympathetic fibres are excitatory, contrary to their effects elsewhere in the bowel. The external sphincter is formed of striped muscle and is under voluntary control. It is innervated by the perineal branch of the pudendal nerve whose fibres are derived from the 4th sacral nerve.

The large intestine receives a mixture of residues left after absorption of products of digestion in the small intestine. Small amounts of digestive secretions, undigested or unabsorbable substances in the food and a large amount of water, constitute the material entering the colon from the ileum. The large bowel removes the water from this mixture and renders its contents into a nearly solid condition. What is left behind is expelled in the form of faeces. The accumulation of matter in the colon after being ejected by the ileum causes the shifting of it by means of mass peristalsis into the transverse colon from which it is returned to the ascending colon by anti-peristalsis. Thus, mixing of the colonic contents takes place.

Three types of movements have been observed in the dog, with the use of balloons and manometers. 1) Segmenting contractions, as in small intestine 2) Haustral contractions in which the colon slides over its contents, first in one direction and next in the opposite one. 3) Kneading movements in which large sections contract while the adjacent ones relax. Peristalsis and antiperistalsis also occur in addition to the above three kinds of movements. All these are confined to the ascending and transverse colon only wherein most of the water absorption takes place. In the case of the human subject however, no activity has been seen on X-ray examination.

Mass peristalsis is a characteristic movement of the colon which causes the propulsion of colonic contents towards the rectum. It occurs at long interval bringing about the filling of the pelvic colon and the descending colon. Mass peristalsis is promoted by entry of food into the stomach (gastro-colic reflex). The

terminal ileum becomes active when food is eaten (gastro-colic reflex). The desire to defaecate immediately after a heavy breakfast in the morning is due to these reflexes. In susceptible individuals, they may be elicited even by the mere smell of food, or by the drinking of water or any beverage. Emotional responses concerned with anger, fear and resentment, affect the motility of the colon. Parasympathomimetic drugs increase colonic activity. Morphine depresses the motor activity of the colon.

Defaecation: Normally the rectum is empty. Mass peristalsis pushes faecal matter into the pelvic colon in which it accumulates and fills the descending colon too, with mass activity being repeated. When pressure inside the pelvic colon or rectum rises above 25 cms of water, the desire to evacuate the bowels arises. The filling of the rectum is consciously felt and makes the individual prepare for emptying the bowel. If the time and the surroundings are inconvenient, the reflex can be voluntarily suppressed. The faecal contents are pushed back into more proximal parts of colon, and the sphincters are closed tonically. If the subject decides to respond to the call to stool, certain voluntary adjustments are made by way of adopting the suitable posture, relaxation of the external anal sphincter and putting forth straining efforts – bringing about powerful contractions of the abdominal muscles with respiratory arrest in the expiratory position and with glottis being closed – in order to raise the intra-abdominal pressure. These willed steps reinforce the visceral reflex initiated by the distension of the rectum. Mass peristalsis results and the entire colon is brought into activity with simultaneous relaxation of the internal anal sphincter. The longitudinal muscles of the distal portions of colon contract powerfully and aided by the mass peristalsis, the colonic contents from the splenic flexure downwards are forced out of the anal canal. The shortening of the bowel including the rectum, on account of the contraction of the longitudinal muscle, draws the large bowel upwards, as it were, so that the faecal mass slides down. The contraction of the muscles of the floor of the pelvis (levator ani) holds it taut, so that the action of the muscles of the colon is rendered more effective in ejecting the faecal mass past the anal canal.

While the defaecation reflex can be suppressed or even reinforced voluntarily to a great extent, certain reflex centres in the hypothalamus, and in the lowest part of the spinal cord – lower lumbar and sacral segments as well as the ganglion cells in the plexuses innervating the distal colon – bring about the smooth progress of the defaecation reflex. Unlike in the case of the micturition reflex, cord injuries do not hinder or interfere with the defaecation reflex which can be still elicited, on account of the integrity of the local nerve plexuses.

In infants, an 'automatic' colon is responsible for defaecation. Voluntary or cortical suppression of the defaecation reflex is absent. This becomes possible only after the baby grows.

Faeces: Normally, the faeces is semisolid in consistency. The term diarrhoea indicates fluid nature of the faeces. The quantity formed in a day on a mixed diet, is between 70 and 170 gms, the solid matter constituting 25 – 30 percent. Vegetarian diet gives rise to a greater quantity on account of the roughage – the insoluble and indigestible residue. Faeces are of approximately neutral reaction or of slight alkalinity and contain insoluble inorganic salts of calcium and iron. Cellulose, fats and proteins comprise the organic matter along with small amounts of digestive enzymes. Bacterial contents amount to half the total protein. Fats may be present upto a fourth of the solid matter; neutral fat is the largest fraction, free fatty acids and even soaps being in lesser quantities.

The colour of the stool is due to stercobilin and the unpleasant odour being mainly that of indol and skatol, the degradation products of tryptophane.

A barium meal X-ray series is a useful diagnostic procedure in any clinical investigation pertaining to the alimentary canal. A suspension in water of radio-opaque material (barium sulphate) is given orally to the patient and its progress is studied by taking X-ray photographs at intervals. The normal timings of the progress of barium meal has been established from a study of a large number of normal subjects. The entire alimentary canal is traversed in about 14 – 16 hours. Gastric emptying is rapid

and almost immediate. Caecum is reached in about $2\frac{1}{2}$ hours, the hepatic flexure in 4 hours and the splenic flexure in 6 hours. Barium sulphate appears in stools in about 24 hours and is completely eliminated in 48 hours at the latest.

The outlining of the various parts of the digestive tract helps the clinician to look for filling defects caused by growths and ulcers.

BODY FLUIDS AND ELECTROLYTES

Many aspects of water metabolism have been touched upon in various contexts in the text. The purpose of this section is to present an overall view of water balance in the body.

The regulation of body water content is a very complex problem. The volume and the distribution of various fluids and electrolytes are influenced by many organs of the body.

Body water : This is the largest constituent of the body and is important and essential for chemical reactions and cellular functions on which life depends. Water also is the means of transport of enzymes, substrates, metabolites, gases, electrolytes, antibodies etc. The following are the basic types of change in body composition :—

- 1) Whole tissue loss (starvation)
- 2) Fat loss (dieting)
- 3) Water loss
- 4) Lean tissue loss (muscular wasting)
- 5) Whole tissue gain (growth)
- 6) Pure fat gain (obesity)
- 7) Water gain (oedema)
- 8) Lean tissue gain (athletic training and convalescence)

Rapid weight changes in an individual usually represent fluctuations of the body water content. The body water is distributed between

- 1) Intracellular compartment (inside the cells)
- 2) Extracellular compartment (outside the cells)
 - a) interstitial compartment (in tissue spaces)
 - b) plasma volume (water in plasma) and Lymph, C. S. F. and Aqueous humor and synovial fluid.

The functional integrity of cell membranes is essential for maintaining constancy of the volume of the compartments as well as their chemical and physiological characteristics.

The body fluid compartments are physiological rather than anatomical entities—i. e.—functional volumes with continuous interchange of water between them.

Water molecules continuously move throughout plasma, interstitial and intracellular volumes.

Intracellular volume is the largest compartment of body water but composed of numerous micro-compartments separated at least by two membranes and a layer of interstitial fluid. Substances cannot be added to or taken away from intracellular compartment without traversing the extracellular compartment.

Daily water exchange: (water balance) — The water intake and water output (per day) of an individual who is in fluid equilibrium are as follows:—

Water intake (in 24 hours):—

- 1) Fluids drunk (water, coffee, milk etc) — 1500 cc.
 - 2) Solid food (varies with composition of diet) — 1000 cc.
 - 3) Oxidation of hydrogen in proteins, fats and CH_2O — 300 cc.
- 100 gms fat on complete oxidation yields — 107.1 gm H_2O
- | | | | |
|---------|---|---------|---|
| starch | „ | — 55.1 | „ |
| protein | „ | — 41.3 | „ |
| alcohol | „ | — 117.4 | „ |

Water output (in 24 hours):—

- 1) Urine — 1500 cc.
- 2) Evaporation through skin and lungs (sweat and insensible perspiration) — 900 to 1200 cc.
- 3) Faeces — 100 to 300 cc.

Large volumes of water are involved in physiological functions every day. The mechanisms for conservation of these fluids are chiefly reabsorption of water by kidney tubules — 168,000 cc. and reabsorption of fluids secreted into gastrointestinal tract — 8400 cc.

Equivalent weight:— (Gm – equivalent) It is the weight which combines with or displaces 1 gm of hydrogen. Equivalent weight of one unit combines with or replaces equivalent weight of any other appropriate unit. $m. \text{Equivalent} = 1/1000$ of a gm. Equivalent. Electrolyte concentration in body fluids is nowadays expressed as mEq/L. This is advantageous with regard to activity (chemical activity) because 1 mEq of a cation or base is that amount of base which will neutralise 1 mEq of an anion or acid.

Conversion formula:

$mEq/L = mgm/100 \text{ cc.} \times 10 \times V \div A.$ (V-Valency; A-atomic weight)

$$10 \text{ mgm Ca}/100 \text{ cc.} = \frac{10 \times 10 \times 2}{40} = 5 \text{ mEq/L}$$

BODY FLUIDS

A) Extracellular fluid;—

Plasma— Water, crystalloids (chiefly NaCl) and dissolved colloids (chiefly protein—7–8%).

Interstitial fluid— approximately same crystalloid composition as plasma. Protein content is very little.

	Plasma	Interstitial fluid
Na ⁺	142	138
Cl [—]	103	108
Bicarb [—]	27	27
Ca ⁺⁺	5	5
K ⁺	5	5

Figures represent mEq.

B) Intracellular fluids;—

Chief cation, K ⁺	— 157 mEq.
Anion, PO ₄ [—]	— 110 mEq.
Bicarb [—]	— 10 mEq.
SO ₄ [—]	— 74 mEq.

Proteins are much more than in plasma (muscles 20%).

The fact that extracellular fluid contains very little K^+ and intracellular fluid, very little Na^+ , is of much significance and under certain clinical conditions, the relative proportion may be seriously altered — In uraemia, K^+ is liberated from the cells — extracellular level increases and may stop the heart beat. In K^+ deficiency, Na^+ may enter the cell and must be replaced by K^+ to correct metabolic alkalosis.

Plasma electrolyte concentration studies give only partial knowledge, since plasma electrolyte concentration may be normal even though there may be a marked deficit in the absolute amount. So, content of body water Na^+ and K^+ must be measured if quantitative data are needed.

Electrolytes Pool (exchangeable Na^+ and K^+)

Total exchangeable Na^+ in body	—3890	mE/L
Extracellular (in 17.5 litres of water)	—2450	„
Intracellular	—1450	„
K^+ Pool	—5030	mE/L
Extracellular	— 94.5	„
Intracellular	—4935.5	„

Figures for Na^+ include that present in bones and may be available for restitution of extracellular Na^+ in states of deficiency.

In conditions of fluid imbalance, these pools may be markedly altered in value.

Permeability of Cell membrane (for exchanges between interstitial and intracellular fluids):—

Permeable

Water
Food material (glucose, amino acids
Metabolites (urea etc.)
Inorganic phosphate ions
Inorganic anions.

Impermeable

Cations
Organic phosphate ions
Proteins (except probably
in liver cells).

Red cell membrane—Permeable to chloride and some amount of Na^+

Tissue cell— Not permeable to chloride and permeable to little or no Na^+ .

The question arises if tissue cell membrane is impermeable to chloride. Probably Cl^- is like Na^+ . Red cell membrane probably is not impermeable to cations like Na and K , since radioactive isotope studies show that Na^+ and K^+ move freely in and out of RBC in circulating blood.

Living red cells, by using energy derived from metabolic processes, actively maintain their normal characteristic cation pattern which is different from that of plasma and when metabolism is depressed or ceases, cations move passively with the concentration gradient.

Blood cations (fresh blood)

RBC (70% water)

K^+ — 100 mE/L of RBC or
144 mE/L of water.

Na^+ — 12 mE/L of RBC or
17 mE/L of water.

Plasma (93% water)

K^+ —5 mE

Na^+ — 142 mE/L of plasma or
155 mE/L of water.

In the RBC, energy for movement of ions for maintaining cation pattern is supplied by metabolising glucose (cyanide does not block this transport). Glycolysis is adequate for this purpose. Probably, cation pattern of other tissues is also maintained in a similar way.

DETERMINATION OF BODY WATER IN DIFFERENT COMPARTMENTS

1) Total body water: Early studies were made by means of dessication of cadaver.

Principle of estimation: An innocuous substance which diffuses freely throughout the water of the body and also passes through cell membranes, is chosen. It should not also be selectively stored in any part of the body or excreted rapidly. Deuterium oxide (D_2O —heavy water) is such a substance. An injection of a known amount of D_2O is given and an interval of

two hours is allowed to elapse so that D_2O is uniformly distributed in the whole of the body water. A sample of plasma is taken and the concentration of D_2O in it is determined. From this, the volume of body water is arrived at. (About 43 L men, 30 L women)

2) Extracellular fluid*: The substance used for this determination should pass through capillary endothelium and become uniformly distributed throughout extracellular water. It should not pass through cell membrane and should not be metabolized or excreted during the period of mixing in the body. Radioactive Na^+ and Cl^- are also used. But some fraction penetrates the tissues and hence, give high values. Inulin, probably is the most reliable of all, but the procedure involved is more complicated. Sodium thiocyanate is easily available and analysis in the body fluid samples is a more simple procedure and so more frequently employed. Values obtained may vary with material used and it is better to consider the extracellular fluid as the dilution space of the particular substance under study rather than as an absolute measure of extracellular fluid volume:—Inulin space; thiocyanate space; sodium space, etc. (*About 17L)

3) Intracellular fluid: The total body water and extracellular volume are determined.

Total body water — extracellular volume = intracellular volume.
The value obtained will depend upon the method used for determining extracellular volume. (30L men and 20L women)

4) Plasma volume:—Dye method:—The dye should be non-toxic; it should not enter RBC or tissue space through capillary endothelium; it should be rapidly distributed throughout circulation and not be rapidly excreted. Evan's blue (T 1824) is suitable for this. The dye is injected and the degree of dilution in plasma is determined. This gives plasma volume (from plasma volume and haematocrit value, total blood volume can be computed).

Other methods: Radio active iodine tagged on to plasma protein is used for plasma volume estimation. Radio iron method for red cell volume determination (see under 'blood').

WATER CONTENT OF CERTAIN TISSUES :—

Tooth enamel—3%	fat—10-30%	Bone—20-25%
Connective tissue—60%	Liver—70-75%	Muscle—75-80%
Nervous tissue—80-85%	Plasma—91-93 %	RBC—60-65%
CSF—99%		

Total body water varies in different individuals and is related to the fat content of body. Body fat and body water are inversely proportional—i e.—Less the fat content, greater the water content, in percentage of body weight.

Lean body mass (the actively metabolising, fat-free, cellular, mass (muscle and visceral parenchyma) is fairly constant in composition and consists of water, about 73%.

In new born infants, the proportion of water is greater—77% of total body weight. In adults, males have higher water content than females. In middle age, fall in body water occurs.

ELECTROLYTES

Electrolyte space : This refers to the volume of fluid, in which the injected electrolyte was apparently diluted—whether it be dilution of electrolyte itself or of the radio activity of isotope, eg.— Na^+ space.

Electrolyte pool : It can be defined as the actual weight of the electrolyte (or mEq) readily available for exchanges between one compartment and another. 100 millicuries of radio Na are injected and 24 hours are allowed to elapse for it to mix uniformly with the entire Na ions in the body. From samples of blood obtained total sodium content (Na^+ pool) is derived.

Average Na^+ pool—2500 to 3000 mEq.

Similarly, K^+ pool is estimated but longer time is allowed for equilibration—3000 to 4000 mEq.

Cations :— Sodium :— Total Na^+ content is 65 gm. (Normally Na is lost in urine and sweat. Normal intake per day is 10 gm). When Na intake is curtailed, urinary Na^+ loss continues though it declines over two days. After this, there is no significant Na^+ loss. When Na^+ is lost from the body, simultaneous loss

of extracellular water occurs, to maintain osmotic equilibrium. Nearly half the osmotic force attributable to electrolytes in extracellular water, is exerted by Na^+ .

Potassium :— With an average diet, potassium deficiency cannot occur since it is present in almost all foodstuffs (intake per day—3 gm, excretion—2.5 gm). 80 to 85% is excreted in urine and rest in faeces (very little in sweat). In the absence of K intake, K loss goes on at the rate of 1.5 to 2 gm. per day, in contrast to behaviour of Na. Excess loss of K from body leads to rise in extracellular bicarbonate concentration and alkalosis. Correction is effected by KCl administration. K^+ is essential for intracellular metabolism of most body cells.

Calcium :—Its metabolism is related to that of phosphate. Serum calcium is 9–11 mgm (5 mEq/L). Gastro-intestinal factors are important in regulating calcium absorption (ratio of Ca^{++} to phosphate in diet, acidity of stomach, and products of fat digestion, have a role to play). Ionized fraction is physiologically an important constituent, essential for functional integrity of neuromuscular system. It is also necessary for coagulation and for the contractility of the heart muscle.

Magnesium :— Serum content of magnesium is 1.4 to 2.4 mEq/L. It regulates neuromuscular irritability, just like calcium. It is an important factor in carbohydrate and protein metabolism and activation of ATP. It is absorbed from the stomach.

ANIONS

Bicarbonate :—Continually formed because of carbon dioxide produced in the body. Its concentration in the body depends upon kidney function. Small amounts are excreted in acid urine and large amounts in alkaline urine. Concentration is increased in respiratory acidosis and metabolic alkalosis. Concentration is reduced in respiratory alkalosis and metabolic acidosis. Normal plasma carbon dioxide capacity (bicarbonate concentration) — 25–29 mEq/L.

Chlorides: Daily intake is 69–260 mEq (2.4 to 9.2 gm) and excretion in urine is 119 mEq/l or 7 gm. Cl^- loss usually accompanies Na^+ loss. Cl^- plays an indirect buffering role in gas exchange (chloride shift). Loss of Cl^- can be compensated for by increase of bicarbonate ions. Such compensation may not occur always. Na^+ loss and hence body water loss occurs. Cl^- loss produces same effects as K^+ loss, a loss of either leading to deficit of other ions. Cl^- deficit leads to metabolic alkalosis. K^+ leaves cells and is replaced by Na and H ions. K^+ is excreted from the body. In K^+ depletion, alkalosis follows because bicarbonate increases displacing cl^- which is excreted.

Phosphates: This is the major anion in intracellular water. Extracellular phosphate is mainly inorganic. It is related to Ca^{++} metabolism in bone. In soft tissues, it is necessary for metabolic processes.

Proteins: These form anions in blood because of its slight alkaline reaction. Na proteinate is a member of a buffer pair.

Sulphate: 1 mEq/L in extracellular fluid.

Organic acid: 4–8 mEq/L in extracellular fluid.

THE KIDNEY

The term excretion means the getting rid of substances which can serve no useful purpose in the economy of the body. These are the end products of metabolism of the different food substances which are absorbed into the blood from the digestive tract. Thus, urea is derived from protein breakdown, uric acid from nucleic acids, carbon dioxide and water from carbohydrates and fats. The last two, however, are not entirely devoid of usefulness. Carbon dioxide is mainly lost through the expired air along with traces of water vapour. The kidneys are the main channel for excreting the usual nitrogenous wastes and water, the skin (sweat glands) being a subsidiary one. The gastro-intestinal tract also plays its role in this (excretory) function by not only bringing about the elimination of indigestible food residues but also secretions of the glands in its walls. Saliva is another vehicle for excretion of water, chloride and urea and also some products of detoxication like sulphocyanides. The liver renders harmful substances innocuous and it excretes them along with bile pigments which are waste products present in bile. The excretory organs also provide the exit for drugs administered and unusual and valueless substances like ketone bodies produced in excess in states of abnormal metabolism.

In the middle of the 19th century, Claude Bernard introduced the term *milieu interieur* (internal environment) and conceived of its importance in influencing the activity of all cells bathed or enclosed by it. It was Walter Cannon who thought of homeostasis which comprised all mechanisms maintaining the constancy of the internal environment as regards its physical nature and chemical constituents. The kidney is an organ very much implicated in homeostasis. By excreting several of the blood constituents in a well regulated manner, the kidney, more than any other organ, acts as a guardian for the internal environment.

THE FUNCTIONS OF THE KIDNEY

A. Those concerned with excretion of substances (mentioned below) in the urine.

1. Waste products like urea, uric acid and creatinine.

2. Water, when it is in excess and tends to lower the concentration of electrolytes — ions — in the internal environment. The excretion of water is strictly regulated. All the same, some quantity of water has to be provided for dissolving the constituents of urine. In an adult, when the water intake is just adequate for the needs of the body, the urine is concentrated — hypertonic — compared with the blood plasma and the extra-cellular fluid. The concentration of the urine by the nephron (renal unit) is directed towards the conservation of water in the body.

3. Inorganic ions like Na^+ , K^+ , Ca^{++} , bicarbonate, phosphates, sulphates. The quantities of these ions which are lost in the urine are also efficiently controlled, in order to maintain their concentrations in the body fluids at optimum levels. The kidney can produce H^+ ions which are substituted for Na^+ ions, when it is necessary to conserve the so-called base (sodium). The synthesis by the renal tubule of ammonia and thereby ammonium ions, is also directed to prevent loss of Na^+ .

4. Drugs introduced into the body for therapeutic purposes. Certain drugs are eliminated mainly through the kidney.

5. Compounds resulting from detoxication of toxic by-products of metabolism, like benzoic acid and ammonia.

6. Physiological substances like glucose and aminoacids when they are present above certain limits in the blood.

B. Incidental to the elimination of various substances listed in (A), are functions associated with the maintenance of the constancy (homeiostasis) of the internal environment with regard to electrolytes, water, glucose etc., as well as the reaction (pH) of blood.

C. The secretion of renin by the juxta glomerular apparatus is a function, apparently, as far as is known now, unconnected with the formation of urine. Renin is indirectly implicated in the release of the adrenal cortical hormone, aldosterone, which has a role in the kidney with regard to the retention of Na^+ and loss of K^+ .

Structure of kidney: This has been worked out to a great degree of detail over several decades, with the result that we know more about the ultrastructure of the kidney than that of other organs. While it is an axiom that knowledge of the structure is

a pre-requisite to the understanding of the function of any organ, nowhere is it better exemplified than in the case of the kidney. It is necessary and worthwhile to describe the structure of the kidney with all the known details. More and more details are being revealed with the advent of technical aids like the electron microscope. There are two kidneys, one on either side, in the abdomen and situated on the posterior-abdominal wall. The organ is of a reddish brown colour and has a capsule. When cut into two, lengthwise, it (fig. 23) shows an outer cortex and an inner medulla which, in man, is divided into twelve conical portions, the pyramids of Malpighi (not shown in the fig). The base of each pyramid looks outwards towards the cortex and its apex projects in the form of a papilla into the dilated commencement of the ureter (the pelvis of the kidney).

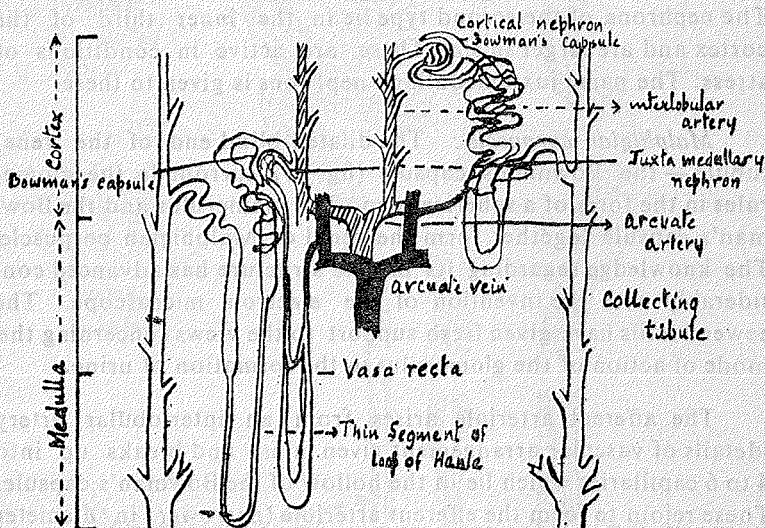


Fig. 23 The Renal Structure

The structural and functional unit of the kidney is the nephron, of which there are about a million in each kidney. The nephron is surrounded by connective tissue and has a rich blood supply. In brief, the nephron, a tubular structure, begins as a dilated portion, the Bowman's capsule, which is invaginated by a

tuft of capillaries, the glomerulus and continued by the proximal convoluted tubule, the loop of Henle, the distal convoluted tubule and the collecting tubule (junctional tubule), a number of which join to form larger collecting tubules, several of which open at the top of the renal papilla (see above) as ducts of Bellini, into the renal pelvis. The length of a nephron is about 3 to 4 cms and if all the nephrons in a kidney are placed end to end, they will extend to 40 miles.

DETAILED STRUCTURE OF A NEPHRON

Two kinds of nephrons occur in the kidney. The first kind lie in the outer $\frac{2}{3}$ of the cortex and is called the superficial or cortical type. 85% of all the nephrons in the kidney are of this variety, which functions normally under all conditions. The nephrons of the second type lie in the inner third of the cortex and are larger in size. These are active in conditions of stress. The name juxtamedullary nephrons is given to these.

Malpighian corpuscle: The dilated blind end of the renal tubule — the Bowman's capsule (fig. 24) surrounds the glomerulus in the form of a spherical cup. The glomerulus and the Bowman's capsule together form the renal or Malpighian corpuscle. The knowledge regarding its minute structure has advanced considerably with the invention of the electron microscope. The newer details have given fresh support to the views concerning the mode of action of the glomerulus in the formation of urine.

The afferent arteriole arises from an interlobular artery (details of vascular arrangement given later) and breaks up into 4 to 6 capillaries which lie in the hollow of the Bowman's capsule. These rejoin to form the efferent arteriole (narrower in diameter than the afferent vessel) which leaves the Bowman's capsule close to the entry of the afferent arteriole. These capillaries (formerly given as 50 in number but now known to be fewer) are embedded in a syncytium of endothelial cells filling the Bowman's capsule. Further, each of the capillary loops gives off branches which anastomose with those of the others. The main capillary loops lie close to the visceral layer of the Bowman's capsule. The endothelial cells of the capillary walls show small pores 0.1μ in diameter, suggesting a filtration function for these. The epithelial cells of the visceral layer are known as the podocytes since they

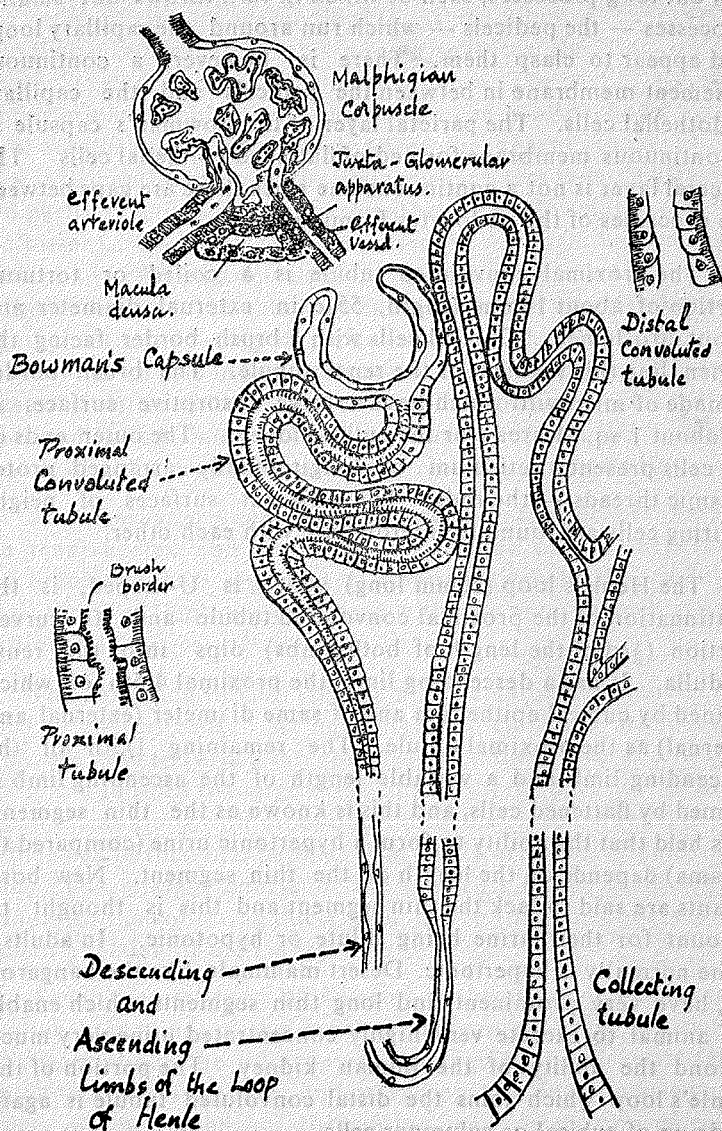


Fig. 24 The Nephron

put out long processes, each of which in turn throws out smaller processes — the pedicels — which run around the capillary loops and appear to clasp them. There is, however, a continuous basement membrane in between the pedicels and the capillary endothelial cells. The parietal layer of the Bowman's capsule is a continuous membrane formed of flattened epithelial cells. The visceral layer is not a continuous one since there are gaps between the processes of the podocytes forming it.

The proximal convoluted tubule is a coiled or tortuous portion of about 14mm length, 55μ in external diameter and about 20μ lumen. Cubical cells with a brush border facing the lumen, line this segment of the renal tubule. The brush border is made of microvilli which have a large absorptive surface, in all about 1 sq. M area (for the entire kidney). The outer ends of the cells present a reticulum of longitudinally arranged protoplasmic threads — the rods. The adjacent surfaces of neighbouring cells are found to interdigitate with each other.

The Henle's loop (20mm long) which is U-shaped, is the continuation of the proximal convoluted tubule and its curved portion ($\frac{1}{3}$ rd of the length of both limbs) dips into the renal medulla. It has a descending limb, the proximal $\frac{4}{5}$ th of which is lined by cubical epithelium and of same diameter (external and internal) as the proximal tubule. The remaining $\frac{1}{5}$ th of the descending limb and a variable length of the ascending limb is formed by flattened cells, and this is known as the thin segment. It is held that the ability to form a hypertonic urine (compared to plasma) depends on the length of the thin segment. New born infants are said to lack the thin segment and this is thought to account for their urine being dilute or hypotonic. In adults, urine normally is hypertonic. Desert mammals, like the kangaroo rat, have very prominent and long thin segments which enable the animal to excrete very highly concentrated urine very much beyond the ability of the human kidney. The portion of the Henle's loop which joins the distal convoluted tubule is again made up of cubical or columnar cells.

The distal convoluted tubule (5mm long) exhibits cubical cells (without brush border) and a short part of it lies in juxtaposition with the afferent arteriole of the glomerulus. The tubular cells in

this region of contact are modified to assume columnar shapes with densely packed nuclei and this gives rise to an elevation on the external surface known as the macula densa. The part of the afferent arteriole in contact with the macula densa also shows structural modification. The elastic fibres are absent, the endothelium is discontinuous and the plain muscle fibres are many layered and partly substituted for by myoepithelial cells forming a cushion (Polkissen). Secretory cells are present in the angle between the afferent and efferent arterioles. Many nerve fibres are also seen in this situation. The tubular element and the vascular element together form the juxtaglomerular apparatus (J.G.A.) which may possibly have a role in the regulation of blood supply to the kidney at least, if not in controlling systemic blood pressure. This will be discussed further, later. The involvement of the JGA in the control of aldosterone secretion is a relatively recent finding.

Juxta medullary nephrons: These lie in the deeper part of the renal cortex and are larger in size than cortical nephrons. The tubules of these nephrons lie almost entirely in the medulla. Their loops of Henle are elongated with the thin segments proportionately longer.

The collecting tubules (called also junctional tubules) are lined by cubical cells. A number of these (one from each nephron) join to form a larger collecting tubule, several of which again join to form the large calibred and short duct of Bellini, which opens along with other ducts of Bellini into the renal pelvis at the apex of the renal papilla. The ducts are lined by columnar cells. The straight course of the segments of the renal tubule along with the collecting ducts give rise to the medullary rays seen in a section of the kidney.

Renal Circulation: While some of the minor details regarding the branching of the renal artery are probably yet to be fully worked out, the following account gives the essential facts which are necessary for understanding the functional significance of the mode of distribution and branching of renal blood vessels.

The renal artery, on entering the hilus of the kidney, breaks up in the pelvis region into five or six branches, which diverge away to run towards the cortico-medullary junction, where each

branch divides and turns to meet the other branches and thereby form the arcuate arteries, which lie parallel to the external surface of the kidney. From the arcuate arteries arise the interlobular arteries running into the cortex. Along the course of each of these interlobular arteries, afferent arterioles arise from it at different points and are given off to the malphigian corpuscle (see above—description of the nephron). The efferent arteriole which leaves the Malphigian corpuscle is said to be narrower than the afferent vessel (though Homer Smith casts doubt on this finding) and it breaks up into a capillary network which surrounds the tubular portion of the nephron. These capillaries drain into venules which join to form larger venous radicles which accompany the larger renal arterial vessels to ultimately give rise to the renal vein which joins the inferior vena cava.

The arrangement and disposition of the arterial supply to the juxta medullary nephrons follows a different plan. The afferent arteriole of the glomerulus arises either from the interlobular artery or even from the arcuate artery itself at an inconvenient angle which somewhat hinders free flow of blood into the glomerulus. The efferent artery which is almost of the same calibre as the afferent artery or even wider, breaks up into a number of straight vessels of rather large diameter—the vasa or arteriolae recta—which dip into the medulla along with the loops of Henle and turn back towards the cortex to drain into venous radicles. On their return course into the cortex, these vasa recta collect themselves into vascular bundles, so that their descending and ascending limbs lie close together and form a vascular counterpart of the hairpin countercurrent system (to be described later).

Trueta, one of the well known renal Physiologists, advanced the view that while ordinarily, renal blood flows entirely through the cortical or superficial nephrons, in cases of stress and other conditions, blood by-passes (partially or even completely) the cortical nephrons and is shunted through the vessels of the deeper or juxtamedullary nephrons. Some anatomists even described a vessel—the Ludwig's arteriole—arising from the afferent artery of the glomerulus and joining straight away the peritubular capillaries, short circuiting the glomerular capillaries. These may be present and even increase in number in chronic renal disease, according to Trueta.

A small fraction of the venous blood from the kidney is drained through the vena stellata under the renal capsule to eventually flow into the peri-renal veins.

Certain significant facts as mentioned below, emerge from the study of renal blood supply.

1. Almost the entire renal arterial flow is channelled through the glomerular capillaries.
2. The blood which flows through the glomerular capillary bed is made to pass through the peritubular capillary bed also.
3. In view of the direct origin of the renal artery from the aorta, a high pressure head is available to drive blood through the renal vessels. The pressure in the glomerular capillaries is as high as 70 mmHg which is very conducive for filtration of plasma to occur as a preliminary to the formation of urine.
4. Glomerular filtration is facilitated by the disparity in the diameters of the afferent and efferent arterioles, the latter being narrower. This feature helps to maintain or sustain a high hydrostatic pressure in the intra-glomerular vessels.
5. Since the volume of blood flow to the kidneys is about 1200 ml., 25% of the cardiac output is available for the extraction of substances to form the constituents of urine. This is a very high turnover and makes the kidney an efficient excretory organ.

While sympathetic vasoconstrictor and parasympathetic (vagus) vasodilator fibres are seen to terminate on the vessels of the kidney, they have no role in influencing the rate of formation of urine.

Autoregulation of renal circulation: It was observed by Rein that the volume of blood flowing through the kidney is remarkably constant. In perfusion experiments conducted subsequently, it was seen that a constancy of flow was maintained

over a wide range of perfusion pressures (80-200 mmHg). Several explanations have been given to account for the invariability of renal blood flow. One hypothesis to explain this was that the level of metabolites controlled the size of the blood vessels. When blood flow was diminished, more metabolites accumulated and caused vasodilatation, so as to allow more flow. When the flow increased, the metabolites were washed away, this in turn resulting in narrowing of vessels.

2) Another view is that intra-renal baroreceptor reflexes may constantly regulate the blood flow. This is suggested by the presence of autonomic ganglia in the renal substance. Sympatholytic drugs did not abolish this autoregulation and so this mechanism is to be somewhat discounted.

3) Pappenheimer and Kinter proposed a rather plausible basis for the constancy of renal flow. The afferent arteriole arises at a right angle to the inter-lobular artery and so plasma skimming may result, the cells being pushed towards the outer cortex and cell-poor plasma only flowing through the glomeruli and the peritubular vessels. Large calibred blood vessels (said to exist) shunt the cell-rich blood in the outer cortex and directly into the venous channels. The concentrated or cell-rich blood exhibits high viscosity and so offers resistance to easy flow. When blood flow is increased or arterial pressure rises, there is more plasma skimming and the haematocrit value of the cell-rich blood rises and offers greater resistance to onward flow. Opposite effects occur with diminution of flow, leading on to renal blood flow being facilitated. Histological studies have failed to detect any haemo-concentration in cortical regions. This seems to knock the bottom out of this postulation.

4) Yet another explanation based on changes in the intra-renal tissue pressure counteracting the renal arterial pressure, has been thought of, but has not found wide acceptance. The intrinsic ability of the vascular musculature in regulating blood flow of the kidney has been invoked as a last resort. Studies on isolated arterial segments lend support to this. Cooling the kidney abolished autoregulation. So also, haemorrhage and anoxia. In view of several theories held, it is most likely that autoregulation of blood flow in the kidney may be the result of many mechanisms in operation simultaneously.

COMPOSITION OF URINE

The daily output of urine ordinarily, ranges between 1 and 1.5 litres. This is, however, subject to the influence of certain factors like water intake, environmental temperature. Drinking large volumes of water will lead to water diuresis — a term indicating greater output of urine. Restricted water intake causes a diminution of urine output. On warm or hot days, since water is lost in appreciable amounts by way of sweat, urine becomes concentrated and smaller in volume. Also, when water loss by way of faeces (diarrhoea) is excessive, urine volume is diminished. On the other hand, urine is voided in larger amounts on cold days. High protein diet increases urinary volume indirectly by raising the amount of urea excreted. Fasting lowers the quantity of urine. Even posture affects urine volume — in the recumbent posture, it is greater than in the standing position. Alterations in the arterial pressure with posture seems to be the underlying cause of these changes. Muscular exercise brings about a reduction in urinary volume. Diuretics can raise the output of urine when desired. $\frac{2}{3}$ rds of the urine formed in 24 hours is excreted in the day time and the rest at night. In children, the urinary volume is proportionately (in relation to body weight) much greater than in adults.

The specific gravity of urine lies between 1015 and 1025 (distilled water — 1000). This is also subject to variation in view of the wide fluctuation in the quantities of the dissolved constituents of urine. Normal urine is almost colourless when produced in large quantities. It may appear straw yellow in colour when seen in bulk in a container. When urine is concentrated, as on hot days or in fever states, it is much darker in colour. The pigment urochrome, mainly and possibly urobilinogen to a lesser extent, impart colour to urine. Urochrome may be a derivative of urobilin. While its output in urine is constant in health, it is increased in amount in fever and hyperthyroidism.. Excretion of excess bile pigment derivatives in jaundice makes the urine highly coloured. Drugs excreted by way of urine may give an abnormal tinge to the urine. So also, presence of unusual derivatives of haemoglobin — porphyrins in urine and in drug poisoning. While adult urine is nearly always hypertonic with

respect to plasma, urine in infants is hypotonic (see above—Henle's loop). The osmolality varies inversely with the output of urine.

The reaction of urine on a mixed diet is acidic owing to the acid metabolites of proteins. Food, predominantly of vegetable origin, makes urine alkaline (alkaline ash diet), while that from animal sources renders it acidic (acid ash diet). Drugs and inorganic salts can alter the pH of urine according to therapeutic needs.

While the actual chemical constituents of urine are of a wide variety, the undermentioned are always found in the urine of normal subjects. The quantities mentioned are only average values and are subject to variation, depending on diet and other factors.

Total water content	95% (W/V)
Solids	5% (W/V)

The solids excreted in 24 hours amount to between 40 and 50 gms per litre.

A. Inorganic substances of urine

Concentration in G/litre

1. Chloride as sodium chloride	9.0
2. Phosphorus as P_2O_5	2.0
3. Total sulphur as SO_3	1.5
4. Sodium as Na_2O	4.0
5. Potassium as K_2O	2.0
6. Calcium as CaO	0.2
7. Magnesium as MgO	0.2
8. Iron	0.003
9. Bicarbonates	0.2

B. Nitrogenous Organic substances:—

The concentrations of urea, ammonia and ethereal sulphates depend on the protein intake. Creatinine and neutral sulphate are unaffected by protein intake.

	G		G
1. Urea	25.0	as nitrogen	10
2. Uric acid	0.6	„	0.2
3. Ammonia	0.6	„	0.4
4. Creatinine	1.5	„	0.5
5. Undetermined N ₂ including hippuric acid, amino acids, purine bases etc.	0.6		—
6. Urinary Indican	0.01		—
		Total	11.7

C. *Other Organic Constituents* :— Pigments like urochrome, urobilinogen, acetone in traces and diastase

<i>Urinary Constituents</i>	<i>Their source in the body</i>
Chlorides } Sodium } Potassium }	food
Calcium	food and bones
Phosphates	Inorganic and organic phosphates of food.
Urea	Protein
Uric acid	nucleoprotein
NH ₃	synthesised in kidney to offset acidosis
Creatinine	muscle metabolism
Hippuric acid	detoxication of benzoic acid in food and conjugation with glycine.
Bicarbonate	synthesised by renal tubular cells and from blood bicarbonate.

Creatine is present in urine in children (during growth), but is normally absent in the urine. Whenever muscles undergo atrophy or degeneration, as in motor neurone disease, it is excreted even in adult urine.

Abnormal urine constituents met with even in ordinary medical practice are — albumin, glucose, bile salts, haemoglobin and bile pigments and their derivatives.

FORMATION OF URINE

The ideas concerning the mode of formation of urine by the renal tubule have become clear, as many of the individual processes involved have been gradually unravelled fairly satisfactorily. It may not be of much real use to recapitulate the older views of Malphigi, Bowman, Ludwig and Heidenhain, each of whom was able to visualise only partially, the mechanism of urine production. Cushney was the first worker to put forward a comprehensive theory and the newer advances in this field have only been additions to Cushney's views and have not supplanted or refuted them. Briefly, the modern concept of how urine comes to be formed, consists of three independent mechanisms, each complementary to the others. They are glomerular filtration, tubular selective reabsorption and tubular secretion or excretion.

In short, the blood plasma, as it traverses the narrow glomerular capillaries, is filtered by the capillary endothelium-visceral layer (of the Bowman's capsule) complex into the potential space of the Bowman's capsule, forming a fluid which is known as the ultra-filtrate in view of the minute size of the pores in the filtering membrane. This fluid is both cell-free and protein-free and holds in solution all the dissolved constituents of plasma. It has the same crystalloid osmotic pressure as well as the reaction (pH) as plasma itself. In the next stage which really determines almost wholly the characteristics of the urine voided, there is a progressive reabsorption of many of the constituents of urine as well as that of water to reduce the volume of urine to sizable proportions. Some substances are completely removed (glucose and amino acids) and some only partially (urea and others), to maintain the concentration in body fluids of essential constituents at a constant level. The tubule in its role of maintaining the acid-base balance of blood and tissue fluids, modifies the urinary fluid by secreting substances to replace those which are to be conserved in the body and not lost. The tubule also secretes potassium, hydrogen and ammonium ions and also certain exogenous substances introduced into the body.

Glomerular filtration: This is a passive process depending purely on certain physical factors. Bowman thought of filtration as a function of the glomeruli. The strongest evidence in support of filtration comes from the micro-puncture technique as practised by Richards and his colleagues in America. The initial work using this technique was performed on the amphibian kidney, but later, these observations were extended to cover the mammalian kidney (guineapig and the rat). The very small samples of fluid from the Bowman's capsule obtained by inserting a micropipette into the capsular space were analysed very carefully by micro-analytical methods. The capsular fluid was found to have the same constituents as plasma excepting for the absence of proteins. This fact conclusively showed that filtration is one of the basic steps in the formation of urine, which of the plasma constituents entered the capsular fluid seemed to depend on the pore size of the filtering membrane as well as the size of the molecules. Haemoglobin, when present in a free state in plasma, passes through the membrane freely. Confirmation of this has been seen in clinical conditions wherein intense haemolysis has led to haemoglobinuria. In conditions like nephritis, albumin can be detected in urine, but the healthy glomerulus seems to prevent the passage of albumin. Thus it follows that the pores in the filtering membrane complex are just large enough to allow haemoglobin molecule to pass through, but not albumin molecule which has a slightly larger size. In pathological conditions, however, albumin can also be excreted, most probably because of a slight increase in pore size caused by pathological processes. Bence Jone's protein has a molecular weight of about 40,000. It can freely escape from the plasma into the capsular fluid. In filtration, therefore, it looks as if the pore size is the determining factor. The recent studies on the structure of the Malpighian corpuscle, have provided further confirmation regarding its filtering function. The visceral layer of the Bowman's capsule is not a continuous membrane and the vascular endothelium has pores in it. The only continuous partition is the basement membrane. Structurally, therefore, there does not seem to be any serious impediment to filtration. So far as is known, there are no clinical conditions in which either globulin or fibrinogen have ever been seen to occur in glomerular filtrate or the urine itself.

As pointed out already, filtration is a purely physical process which does not need expenditure of energy. The difference between the oxygen contents of afferent arteriolar blood and that of the efferent arteriole is almost negligible. On the other hand, alteration of pressures involved in filtration, profoundly affects the filtration rate.

The factors that have a direct bearing on filtration are the hydrostatic pressure of blood in the glomerular vessels, the colloidal osmotic pressure in the glomerular capillaries and the hydrostatic pressure exerted by the fluid present between the two layers of Bowman's capsule. Thus, the formation of glomerular filtrate is similar to those of tissue fluid and lymph. Measurements of the blood pressure (hydrostatic pressure) in the afferent arterioles have been made in the frog's kidney directly by Heyman and indirectly in the dog by Winton. Because of the direct origin of the renal artery from the aorta, the high head of pressure in the former vessel is not dissipated much, by the time blood reaches the afferent arterioles. The estimates of pressure in the afferent arteriole yield values about 75 mm Hg. Colloidal osmotic pressure is usually around 25 mm Hg. Pressure in the Bowman's capsule has been estimated to be around 5-10 mm Hg. The net filtration pressure will be :

Blood pressure in the afferent arteriole — colloidal osmotic pressure of blood — Hydrostatic pressure in the Bowman's capsule.

Substituting the numerical values for the various pressures, the net pressure available for filtration will be :—

$75 - 25 - 5 = 45$ mm Hg. This value of 45 mm Hg is more than adequate to account for efficient filtration. Changes in any one or more of the three pressures that affect glomerular filtration have been seen to influence the rate of filtration. Thus, a fall in general blood pressure as occurs in haemorrhage and other conditions, will result in cessation of filtration, since the driving pressure for filtration is very much lowered. Intravenous saline transfusion causes a reduction in the osmotic pressure of plasma because of haemo-dilution. Hence filtration pressure

increases and the rate of filtration is increased. In experimental studies involving blocking of the ureter, urine flow stops. Such blocking raises the tubular pressure and eventually the capsular pressure which becomes very high, opposing filtration.

Tubular Re-absorption : It has been firmly established that tubular re-absorption is a major process modifying the glomerular filtrate both quantitatively and qualitatively. The final characteristics of urine, both physical and chemical, are almost solely determined by tubular re-absorption since the glomerular filtrate is of an invariable concentration and volume normally, being dependent only on physical factors like hydrostatic and colloidal osmotic pressure which do not suffer changes in the normal course of events. Quite an impressible array of evidence has been gathered to furnish support for reabsorption as a function of the renal tubule.

The structural features of renal tubule which vary from one part to the next are indicative of a reabsorptive function. This is especially so with regards to the so-called brush border epithelium of proximal convoluted tubule. The microvilli possessed by these cells in their luminal surface are characteristic of cells which have an absorptive function. It is very plausible that the other parts of the tubule also share in this function.

The volume and the chemical composition of urine as compared with the glomerular filtrate, offers the most dramatic evidence of reabsorption. Of the 120 ml/minute or 170 litres/24 hours of the glomerular filtrate, only about 1 cc/minute or 1.5 litres/24 hours is excreted as urine. Urine is hyper-tonic in adults and this implies the transport of water by the renal tubules from their lumen. Glucose and bicarbonate which are always found in the glomerular filtrate are absent in urine. Amino acids and vitamin C which are present in the glomerular filtrate are found in very small quantities in urine. The glomerular filtrate is alkaline in reaction like blood plasma, whereas urine on a mixed diet is on the acid side of neutrality. Many dissolved constituents of the filtrate are found to be present in urine in much higher concentration. These facts show that the various substances are selectively absorbed, each to a different degree.

TABLE

Constituent	Plasma, amount in 100 cc.	Urine, amount in 100 cc.	Concentration in kidney, No. of times.
Water	90-93 %	95 %	—
Proteins, fats and other colloids	7-9 %	—	—
Glucose	100 mgm.		
Urea	30 mgm	2000 mgm	66
uric acid	3 mgm	50 mgm	17
creatinine	1 mgm	100 mgm	100
Na ⁺	320 mgm	350 mgm	1
K ⁺	20 mgm	150 mgm	7
Ca ⁺⁺	8 mgm	15 mgm	2
Mg ⁺⁺	2.5 mgm	6 mgm	2
Chloride ⁻	370 mgm	600 mgm	2
Phosphate ⁻⁻⁻	9 mgm	270 mgm	30
SO ₄ ⁻⁻⁻	3 mgm	180 mgm	60

The analysis of a sample of fluid collected from different parts of renal tubule by Richards and others in the frog's kidney as well as in the mammalian kidney, showed that different substances were absorbed in different parts of the tubule — eg. — glucose in proximal tubule.

Phloridzin, when injected, suppresses glucose reabsorption without affecting that of other substances including water. The fact of selective reabsorption is supported by this observation. Poisoning of enzymes by the cyanide radicle results in a large increase in the urine volume, which however, is less than the total glomerular filtrate per day. Cyanide seems to abolish active reabsorption, but does not materially affect passive reabsorption.

Diuretics, which increase glomerular filtration and tubular flow, cause the formation of dilute urine of large volume with an increase in the total urinary urea and chloride. The rate of flow of fluid in the tubule determines the rate of reabsorption. If the

former is rapid, less reabsorption will take place. On the contrary, obstruction to flow of tubular contents raises the absorption rate. Partial obstruction to the ureter on one side increases the concentration of urine on that side, though urinary chloride was less than on the other side. This implies greater reabsorption of salt and water.

Whenever tubular reabsorption was found to be increased, there was a concomitant increase in the oxygen consumption of the kidney. But the oxygen utilisation of the Malpighian corpuscle, on the other hand, has been shown to be a negligible fraction of the total oxygen consumption of the kidney.

The mechanisms underlying reabsorption: This is carried out in two ways — passive reabsorption and active reabsorption. When the transfer of substances is effected by a concentration or an electrical potential gradient between the lumen of the tubule and the interstitial fluids, the reabsorption is said to be passive. But work will have to be performed to raise the concentration in the tubule by removal of water from it or to set up a potential gradient by moving one type of ion. Urea and chloride are examples of substances moved across passively. In the former case, a concentration gradient is set up and a potential gradient in the latter case.

Active reabsorption implies the movement of a substance involving a carrier mechanism which requires energy derived from metabolic (oxidative) reactions.

Sites of reabsorption of various substances:

1. **Water:** — 80-85% of water is reabsorbed passively (obligatory moiety) in the proximal convoluted tubule. This is unchanged in all conditions. 15-20% is reabsorbed in the distal convoluted and collecting tubules. How much of the 15-20% is reabsorbed actually, depends on the blood level of the antidiuretic hormone and hence the term, 'facultative reabsorption' implies the variability of the amount of water reabsorbed.

2. The entire glucose content of the glomerular filtrate is removed (actively) in the proximal convoluted tubule, provided the carrier mechanism is not saturated. (Further details on glucose reabsorption are given later).
 3. Sodium ions are taken up (actively) mostly in the proximal tubule and the rest in the distal part of the tubule.
 4. Chloride is passively reabsorbed in the proximal part and actively in the distal part of the tubule.
 5. Potassium ions are reabsorbed in the proximal part and are excreted or secreted in the distal part.
 6. Phosphates are taken up in the proximal tubule.
 7. Bicarbonate is removed to the extent of $\frac{4}{5}$ th in the proximal part and the rest in the distal tubule.
 8. Urea — part in proximal tubule and rest in the distal tubule.
- To sum up, proximal tubular portions are responsible for the reabsorption of 80% of water, whole of glucose, phosphates, large amounts of sodium, bicarbonate, chloride and some fraction of urea. The distal tubule accounts for 15–20% of water, sodium, chloride, bicarbonate and ammonia.

The glomerular filtrate is isotonic with plasma and the contents of the proximal segment are also isotonic or slightly hypotonic. Hence, the fluid reabsorbed in this part of the tubule is also isotonic, the chloride and the bicarbonate varying inversely in relationship to each other. Their total content is constant and matches that of sodium. In the descending limb of the loop of Henle, isotonicity is most probably maintained since its walls are highly permeable to water molecules. In the ascending limb however, owing to the removal of sodium, the tubular fluid becomes hypotonic (half the osmotic pressure of plasma). In the distal convoluted tubule, if water loss is to be promoted in conditions of water logging of the tissues, further dilution occurs by the abstraction of sodium from the lumen of the tubule. If water is to be conserved, it is absorbed in this part of the tubule so as to concentrate the urine. Further concentration occurs in the collecting tubule. But this requires the presence of adequate amounts of the antidiuretic hormone. The fluid that leaves the collecting tubule in the event of maximum concentration of urine, has a content of 1400 m.osmol/litre (plasma —

285 m. osmol/litre). In the lines to follow, the active reabsorption of many substances is considered, with glucose as a typical case since more is known with regard to this substance than others. Glucose is an organic compound and does not ionise. It is transported by the tubular cell (proximal convoluted part) from the lumen to the interstitial fluid and thence to blood against a concentration gradient. Of the total quantity of glucose entering the proximal convoluted tubules in all nephrons—amounting to more than 100 mg per minute—normally the whole of it is reabsorbed, leaving very little (this cannot be detected in the urine with Benedict's reagent) or practically nothing. When, however, the plasma concentration is increased gradually, glucose still will not escape in the urine till a certain plasma concentration is attained. With further rise in plasma glucose level, more and more glucose will be lost in the urine. This indicates that there is a carrier mechanism of a limited capacity involved in the reabsorption of glucose and it is indicated schematically as follows:



K — carrier ; G — glucose carried over.

The carrier K combines reversibly with glucose in the tubular lumen, the actual combination taking place at the cell membrane of the tubular cell. Only in the combined form glucose can pass through the cell membrane which is impermeable to glucose in the free state. Once glucose enters the cell interior, it is set free from the carrier to pass into the extracellular fluid around the tubule. In the scheme given above, it is not exactly known which step requires expenditure of energy to make the absorption an active process. The action of the carrier is like that of an enzyme. A cell taking part in transporting substances can effect simultaneously, the transfer of a number of substances. A few substances can even share the same carrier as in the case of amino-acids. Even though the physical chemistry of carrier mechanism has been unravelled to some extent, the exact chemical nature of any carrier has not yet been revealed. Just as certain chemical and physical agents inhibit enzymes, there are substances which can render the carriers ineffective. For example, phloridzin, a glycoside, interferes with the transport of glucose (phloridzin

diabetes). Glucose reabsorption ordinarily is completed in the upper part of the proximal convoluted tubule when the plasma level and hence the filtrate concentration of glucose, is within the usual limit.

From studies made relating plasma levels of glucose with the excretion of glucose in urine, it has been concluded that the carrier mechanism is fully loaded when it transports about 375 mg (for males) per minute, from the tubular contents to the blood. The figure is higher in the male than in the female (300 mg). This value of about 300 mg is designated as the Tubular maximum TmG. The glomerular filtration rate ordinarily is 125 ml/minute and at this rate if plasma concentration exceeds 300 mg %, the excess of glucose should be excreted. But it has actually been observed that even before the plasma concentration approaches 300 mg (even at 200 mg), glucose appears in the urine. The maximum rate of absorption is not attained until the plasma concentration is raised above 300 mg. These observations can only be explained by the possibility of disparities in the efficiency of the different nephrons. The relation between the filtering capacity and the ability to reabsorb glucose may not be the same for all renal units. Some glomeruli may pass down more glucose than can be absorbed in the tubular portions and other glomeruli may allow less glucose to enter the tubule than what is needed to saturate the absorptive capacity.

According to hitherto well-established notions, all substances passing through the kidney were divided into threshold and nonthreshold substances. Glucose, amino acids and water were among the threshold substances. These were said to appear in the urine only when their plasma concentrations exceeded a certain critical value (one for each substance) — the renal threshold. Nonthreshold substances like urea and uric acid were always found in the urine no matter what their plasma levels were. Recent studies have dispelled the idea that for a substance to appear in urine, its concentration should exceed a definite limit. In diabetes mellitus, glycosuria is a very important feature. Even though blood glucose level is above the normal limits, glycosuria need not be explained merely by the glucose

level rising above the renal threshold value of 180 mg%. The filtration rate and the plasma glucose concentration, the tubular capacity for reabsorption are all factors to be reckoned with in diabetic glycosuria.

Reabsorption of water: The amount of water lost through the kidneys in the form of urine is dependent, among other things, on the intake of water and salts. The volume of water excreted is accurately adjusted to maintain the normal osmolarity of the body fluids. The value in normal plasma is 285 milliosmolals. If water intake is high, then urine volume will be correspondingly more, and the urine comparatively dilute. If water intake is restricted or water loss by other channels (lungs and sweating) is excessive, urine will be of a small volume and hypertonic or concentrated. The kidney has a remarkable ability to modulate the volume of urine in accordance with bodily needs for water. Homer Smith explained the basic processes underlying water reabsorption. From his studies on the functioning of the renal tubule, he concluded that reabsorption of water occurs in two stages. The first of these, he termed obligatory reabsorption, meaning thereby that the quantity of water absorbed is constant and invariable under all circumstances. 85% of the water of the glomerular filtrate is reabsorbed by this means in the proximal convoluted tubule and ordinarily, the rest of the 15% of the glomerular filtrate which escapes reabsorption in the proximal tubule is absorbed in the distal convoluted tubule. This is known as the facultative moiety, since the exact amount of water reabsorbed by this mechanism is subject to change, according as water has to be conserved (when more water is reabsorbed) or has to be excreted (when less water is reabsorbed increasing the urinary volume above 1-1.5 litres). It is the second mode of reabsorption (facultatory) that is under the influence of the antidiuretic principle of the neurohypophysis. Verney was primarily responsible for elucidating the role of the antidiuretic hormone. He attributed the regulation of the secretion of the antidiuretic hormone to the action of certain osmoreceptors in the supra-optic and the paraventricular nuclei of the hypothalamus. These are nerve cells which have evolved sensitivity to changes in the crystalloid osmotic pressure of blood. When there is a fall in the crystalloid osmotic pressure, as by water

logging of the body and hence dilution of blood, the osmoreceptors swell up by abstracting water from the surrounding tissue spaces. This, so to say, depresses their activity and in turn results in the abolition or diminution of the release of the hormone. If there is a rise in the crystalloid osmotic pressure as happens with greater intake of salts or excessive loss of water by way of perspiration on a hot day, the osmoreceptors lose water to the extra-cellular spaces and thereby are excited. This results in greater output of the antidiuretic hormone. Verney drew the above conclusions from his experimental studies, in which he injected saline of different concentrations into the internal carotid artery of a dog and thereby produced urine of different volumes and concentrations.

Reabsorption in the proximal tubule : This is a consequence of the active outward transport of sodium in this part of the nephron. Sodium draws chloride, along with it to maintain equality of electrical charges on the two sides of the tubular epithelial cells. The rise in the osmotic pressure of the peritubular fluid, when sodium and chloride enter it, causes water to be drawn from the tubule in a passive manner. This mode of reabsorption of water, as mentioned above, is responsible for the diminution of tubular contents by about 85% of their initial volume. It can be appreciated that the fluid absorbed from the proximal tubule is itself isotonic with plasma, since solutes and solvent are absorbed together.

Absorption of water in the rest of the tubule : The descending limb of the loop of Henle is freely permeable to water, with the result that there is a free exchange of water between the extracellular fluid and the tubular contents. Any inequalities as regards osmotic pressure, are evened out. But, as the fluid flows through the ascending limb, sodium is removed from the tubular contents, the fluid reaching the distal convoluted tubule becoming very hypotonic in relation to plasma. Whether or not there has to be subsequent concentration of the urine, depends on the level of the antidiuretic hormone. In adequate amounts, the hormone brings about water reabsorption in the distal convoluted tubule as well as in the collecting tubule by rendering the walls highly permeable to water which escapes into the peritubular space

under osmotic attraction of the highly hypertonic environment. The resulting urine is concentrated and hypertonic in respect of plasma. On the other hand, if sufficient amounts of hormone are not released, the urine that leaves the distal tubule passes through the collecting tubule without appreciable further concentration. Urine thus formed, is dilute.

Normally, about 25 litres of water are reabsorbed in 24 hours in the distal and collecting tubules. This, by itself is a passive process. The driving force for absorption of this large amount is derived from the hypertonic state of the fluid surrounding the collecting tubule. Wirz and his co-workers attributed the maintenance of a high concentration of sodium in the peritubular fluid to the functioning of a *hairpin countercurrent multiplier system*, which is essentially composed of the loop of Henle of the juxta medullary nephron with its descending and ascending limbs. The tubular fluid runs towards the medulla in the descending limb and in the opposite direction in the ascending limb. The loops of Henle of these nephrons are confined to the medullary region. The loops of Henle of the deeper nephrons have all the requisites for the efficient operation of countercurrent system and in addition have a vascular counterpart, the vasa recta. The descending limb has walls freely permeable to water (and also assumed to be to salt), while the walls of the ascending limb are permeable to only sodium but not water. The vasa recta of deeper nephrons are taken to be the necessary vascular counterparts of the tubular countercurrent system, since the former also dip deep into the medulla and turn backwards to run towards the cortex, (like a hairpin). The vasa recta are essential to keep the operation of the countercurrent system going on continuously.

The basic principle of a hairpin countercurrent system is now presented—Two tubes having walls permeable to a particular solute, are laid side by side in contact with each other and solutions (aqueous) of the substance (say salt) to which the walls are permeable, are made to run in opposite directions in the two tubes. If the concentration in one is greater than in the other (fig. 25), the salt will pass into the latter all along the line of contact between the two tubes. It follows that the concentration

of salt will gradually fall in the first tube as fluid passes along its interior. Likewise, the concentration will rise continuously in the fluid as it traverses the second tube. If the two tubes are joined, as shown in the lower part of fig. 25, a U-shaped or hairpin system will result. Only one more assumption will have to be made—a driving force for transferring the salt from the first to the second tube should operate—since a simple concentration gradient as a driving force will not be effective in such a system. It will follow that in such a set up when a steady state is established, the concentration of the salt will attain a high value at the bent portion of the U-tube. In the lower tube, concentration rises steadily and in the upper one it falls. The very high degree of

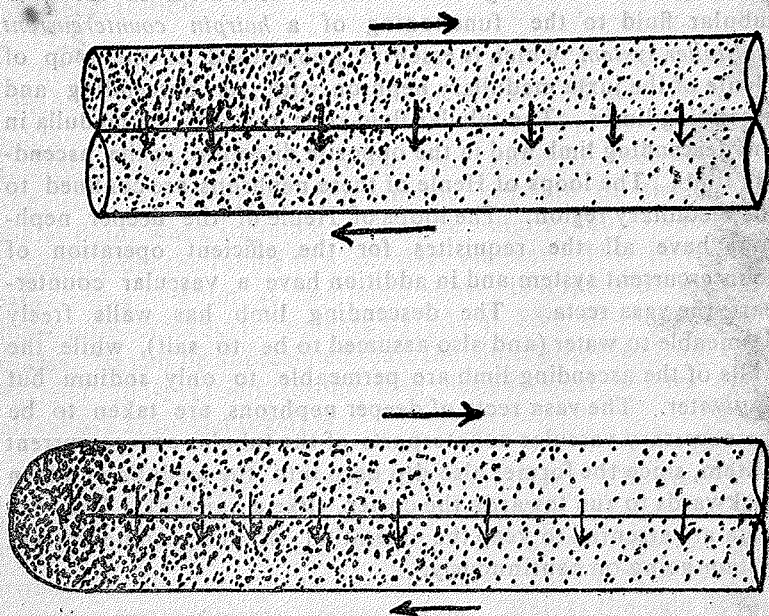


Fig. 25. *Countercurrent Hypothesis*

The density of stippling indicates the concentration of the solute. The arrows shown outside the tubes denote the direction of flow of fluid in the tubes. The arrows crossing from the tube above to the one below show the direction of transfer of solute passively (upper figure) and actively (lower figure).

concentration at the bent portion cannot be achieved otherwise than by the countercurrent system. The concentration of salt at the bent portion is much greater than that of the fluid entering or leaving the system and the disparity is much more than the difference, between the concentration at the point of entry and that of exit from the system, which is the same as at any point along the tubes. In other words, the effect of a simple transfer system of the model (upper part of the fig. 25) is multiplied several times in the countercurrent system (lower part of fig) —hence the term countercurrent multiplier system. Comparing the model described above with the loop of Henle (acting as a countercurrent multiplier), the descending limb takes the place of the lower tube and the ascending limb that of the upper tube. Here, there is no direct contact between the two limbs which are separated by extracellular or peritubular fluid. But this does not invalidate the parallelism between the model and the loop of Henle. Thus, the loop portion (bent part) will accumulate salt in it. Consequently, the peritubular fluid also will show similar hypertonicity, since the transfer of salt from the ascending to the descending limb will have to take place via the peritubular fluid which occupies the space between the two limbs. There is a continuous fall in the osmolality of the extracellular fluid towards the cortex. There are said to be concentric shells (each homogeneous in itself—of same concentration throughout), each of different osmolality, the highest being in the medulla and the lowest in the cortex, there being a fall between one shell and the one immediately external to it. By making serial sections of the kidney substance and studying the formation of ice in them, while cooling them, it has been confirmed that the osmolality (concentration in the peritubular and tubular fluid) falls gradually from the medulla towards the cortex. This is more or less irrefutable evidence in favour of the countercurrent hypothesis.

It has been tacitly assumed that the maintenance of a hypertonic environment in the medulla, is due to the functioning of a hairpin system solely in the Henle's loops of the juxtamedullary nephrons. Whether the cortical nephrons do contribute their mite in this regard, is not quite clear. These nephrons are mostly confined to the cortex with only the extreme tip of their

Henle's loops entering the medulla. Further, the blood vessels of the cortical nephrons do not have the hairpin configuration like the vasa recta of the deeper nephrons. It is also remarkable that the deeper nephrons which are in a minority, have a major share or even are solely responsible for the maintenance of the hypertonicity of peritubular fluid in the medulla.

The significance of the above-described mechanism is with regard to the concentration of urine after it leaves the loop of Henle. The distal and collecting tubules are inherently impermeable to water. As the tubular fluid enters the distal tubule, it is hypotonic. Some amount of water may be reabsorbed in the distal tubule, but the urine entering the collecting tubule is still dilute. Concentration to render urine hypertonic can occur only if more water is removed from the contents of the collecting tubules. In the presence of the antidiuretic hormone, collecting tubules become freely permeable to water and because of their medullary location (most of their length lies in the medulla), the highly concentrated peritubular fluid brings about osmotic diffusion of water outwards, leading on to diminution of urine volume and its becoming hypertonic in respect of plasma. The vasa recta which are present in the medulla, carry away the surplus water removed from the collecting tubules so that the hypertonicity of the peritubular fluid is not dissipated by the entry of water from the collecting tubules. Unless the blood vessels remove the excess of water in time, such a concentrating process as described above will grind to a halt very soon.

It is a matter of particular interest in this context, that in desert mammals like the kangaroo rat, the loop of Henle in the kidney is very long. This animal excretes urine which is many times more concentrated than the urine of man. In fact, a remarkable feat of adaptation is that the kangaroo rat does not need to drink water as such, at any time. The metabolic water is quite adequate for its needs and hence it has to be very rigidly conserved in the body. The necessity for it to concentrate urine to a much higher degree than other animals, is obvious. The great length of the Henle's loop in the animal, offers indirect confirmation of the countercurrent hypothesis.

There is wide acceptance of the views of Wirz as regards the mode of concentration of urine in the collecting tubule.

Renal function in the foetus: The kidney does function as an excretory organ in the foetus. The new born baby passes urine immediately after birth. The amniotic fluid is considered by some, to be at least partially made up of foetal urine. The glomeruli are crowded in the kidney of the new born infant and the loop of Henle, especially the thin segment, is poorly developed. The urine is found to be markedly hypotonic. The volume is low (20 ml) at birth. Upto three months of age, there is no diuresis in response to drinking of water which is eliminated slowly. The specific gravity is low and so also the osmotic pressure. These characteristics are thought to be the result of the shortness of the loop of Henle. The antidiuretic hormone, if administered to very young babies, seems to have very little effect. The neurohypophyseal tissue at this age, seems to be poor in its hormonal content. All the indices of renal function (see further down) are low. The glomerular filtration rate (as measured by the inulin clearance) is only 30 cc/sq. M body surface (adult-75 cc). The diodrast clearance is only 1/10th of the adult value, making due allowances for difference in body surface area. The filtration fraction is high, suggesting that the tubules are less efficient than in adult. Urea clearance is also low. The values characteristic of an adult are attained only towards the end of the first year of age. One could consider these facts as additional proof for the validity of Wirz's views.

The share of different parts of the tubule in the concentration of the urine is shown percentage-wise.

Water of glomerular filtrate
absorbed as percentage.

Proximal tubules	80
Loop of Henle	6
Distal tubules	9
Collecting ducts	4
Passing into the urine	1

The reabsorption of certain substances like sodium, potassium and others, is discussed separately, since these are not only reabsorbed but also secreted.

Secretion : This process brings about the transfer of solutes from blood or peritubular fluid into the tubule. The term tubular excretion is synonymous with secretion. While certain ions are among those secreted by the tubular epithelium, certain chemicals of extraneous origin are eliminated mainly by tubular excretion. Phenol red is the best example and it is eliminated from blood to a great extent, by secretion. Hippuric acid (benzoic acid conjugated with glycine), like other products of detoxication is also secreted into the tubular lumen. Substances used as contrast media in certain investigations – eg. – diodrast- are also dealt with by the kidney in this way. So also penicillin, the antibiotic. The secretory activity seems to occur in the walls of the proximal tubule as well as in the distal tubule. Secretion is the converse of active reabsorption. A carrier mechanism working in reverse, transporting a substance from blood to the tubular lumen, is held to be responsible for dealing with each substance actively eliminated. The carrier action in secretion is similar to that involved in reabsorption, in all respects. Para-amino hippuric acid is notable in that, almost the entire plasma content is extracted from plasma to be delivered into the tubular lumen. Hence its rate of elimination is used as a measure of plasma flow to the kidney. Some of these related aspects of kidney physiology are dealt with, separately.

The main evidence in support of secretion, has been derived from the fact that the quantity of a substance excreted in unit time from the blood plasma exceeds that which is present in the glomerular filtrate formed in the same period. In other words, the excretion rate (clearance) is greater than what can be accounted for by mere filtration in the glomeruli. This will be elaborated further, below.

Reabsorption and excretion of Sodium and Chloride : Sodium ion is the most important of the extracellular constituents because of its contribution to the maintenance of the crystalloid osmotic

pressure (very little colloid or oncotic pressure exists in extracellular fluid). Thus, the regulation of its concentration is a very significant aspect of homeostasis. Most of the sodium in the glomerular filtrate is actively reabsorbed in the proximal tubule by means of a carrier mechanism which is shared with potassium. The actual mode of functioning of a carrier and its chemical identity are points yet to be elucidated. The active removal of sodium leaves an excess of anions in the tubular fluid and to offset this, chloride ions also leave the tubules.

In the more distal parts of the tubule, sodium is absorbed against a steep gradient, the ion almost disappearing from urine and chloride may even be shifted by an active process in the parts of the tubule beyond the proximal segment. Chloride may not accompany sodium which is substituted for, by potassium ions secreted into the lumen. The actual mode of sodium absorption in the distal parts of the tubule has not been revealed yet. An exchange of sodium for potassium seems to be involved in the carrier mechanism.

A few lines may be necessary to indicate the regulation of sodium excretion. Normally, only 0.5% of the sodium content of the glomerular filtrate is excreted in a day. If there is a sudden change in the glomerular filtration rate, sodium excretion also undergoes increase for a short duration. Changes in the filtration rate maintained for prolonged periods, bring about compensatory alteration in the reabsorption rate so that the amount excreted is not appreciably altered.

Adrenal steroids like aldosterone and even glucocorticoids (though the latter has a feeble action, yet, in view of their much larger daily output, cannot be ignored) exert their effects on the tubule in the regulation of sodium excretion. While glucocorticoids bring about a rise in the glomerular filtration rate in addition to a weak direct effect, aldosterone, the principal mineralocorticoid, causes a reabsorption of sodium along with chloride and also an uptake of sodium in exchange for potassium. Renin released from the juxtaglomerular apparatus, is intimately concerned with aldosterone secretion. A negative feed-back type

of relationship may exist between renin and aldosterone. When blood volume shrinks, renin is released and eventually aldosterone output is increased (see in section on endocrinology under adrenal cortex) and thereby a greater degree of sodium and water reabsorption takes place, which leads on to expansion of blood volume, making further release of renin unnecessary. Aldosterone accelerates the synthesis of some protein, presumably a carrier taking part in sodium transport. It is also believed that the hormonal action is only in the form of a fine control of sodium reabsorption which can go on even in the absence of the hormone. Exogenous aldosterone administered to a subject causes withholding of salt for a very short while but later, other compensatory adjustments increase glomerular filtration to counteract the influence of the hormone. Administration of a large volume of salt solution diminishes the reabsorption of salt in the proximal tubule, most probably by provoking the release of a humoral factor, to antagonise the action of mineralocorticoids. When osmotic diuretics like glucose (as in glycosuria), urea etc., increase the volume of urine, sodium reabsorption is decreased. Sodium excretion is increased when either exogenous or endogenous or both types of anions, are increased in urine. Mercurial diuretics, chlorthiazide, sulphacetamide etc., inhibit sodium reabsorption.

Excretion of Potassium : This ion is both reabsorbed and secreted by the renal tubule, the amount found in the urine derived mainly from secretion. Most of the potassium in the filtrate is actively reabsorbed before the tubular fluid reaches the distal convoluted tubule where secretion occurs. Potassium enters the tubule in exchange for sodium. The carrier mechanism handles both the ions transporting them in opposite directions. The amount of potassium lost in urine, in terms of concentration, seems to depend, strangely enough, on the concentration of sodium. It is inversely related to the concentration of H-ions which are set free by the tubular cell to replace sodium and potassium, as a step in conserving these valuable cations.

Urea : This is the chief waste product of urine and is present in the highest concentration of all solutes in urine. Because it can pass through the cell membranes with facility, an attempt by

the tubule to concentrate urine with regard to urea may fail, by urea diffusing out, but the renal tubule, in parts at least, is somewhat impermeable to urea unlike cell membranes, in general. The anti-diuretic hormone makes the tubular wall more permeable not only to water, but also to urea. Therefore, there must be a means of isolating the urea (in high concentration) in the tubule and preventing its escape out of the tubule into the peritubular fluid. The amount of urea lost in urine depends on the rate of urine flow, upto a limit. The maximum urea excretion is achieved when the flow rate of urine is 2 ml/min and no further rise occurs unless osmotic diuresis also occurs, when at least $\frac{2}{3}$ rds of the urea filtered, is excreted. When urine flow diminishes again, a lower limit in urea excretion is reached — about $\frac{1}{5}$ th of the urea filtered is excreted. The changes in urea excretion are mainly due to changes in the degree of reabsorption of urea in the distal tubule and the collecting tubule. Only the proximal tubule does not show any change as regards the amount of urea reabsorbed and it accounts for the absorption of 30-40% of the filtered urea. The distal tubular action depends, just as in the case of water, on the levels of the antidiuretic hormone. In water diuresis, reabsorption in the distal tubule is negligible, but the proximal segment reabsorbs about 30-40%. In osmotic and water diuresis occurring together (see further on for diuretics), reabsorption of urea is decreased. When urine volume is diminished, at least $\frac{4}{5}$ ths of the urea is reabsorbed. This increased reabsorption seems to be due to the action of anti-diuretic hormone which acts on the distal and collecting tubules, to make increased urea reabsorption possible. The action of the hormone is similar to that with regard to water. The distal and collecting tubules become more permeable to both water and urea. But, urea that escapes into the peritubular spaces, is not carried away by the vasa recta, as in the case of water (see counter-current system), but the high urea concentration in the peritubular fluid has no importance in the operation of the countercurrent mechanism since there is very little osmotic gradient between this fluid and the tubular contents.

QUANTITATIVE ASPECTS OF RENAL PHYSIOLOGY

The idea of Clearance : The assessment of kidney function in relation to its ability or capacity to excrete any particular

constituent of urine, is made in terms of the clearance of the substance. The clearance of any substance is that volume of plasma which is completely cleared of it, in a minute, by elimination in urine. Alternatively, it is the volume of urine which normally contains the quantity of a given substance that is excreted by the two kidneys, in a minute. Though no part of the plasma is at any time completely depleted of any of its constituents by loss in urine, for the formation of which the entire plasma has to part with a little of every constituent, the idea of clearance is a highly useful one in that it enables to quantitatively assess the function of the kidney in excreting any one of its numerous dissolved substances.

The concentrations of the substance in the blood and in the urine as well as the rate of flow of urine are determined in order to arrive at its clearance value.

- U — Concentration in the urine
- B — Concentration in blood
- V — Urine flow per minute

Clearance is given by the formula $\frac{UV}{B}$ (ccs of plasma)

In addition to others, the determination of urea clearance is a standard test in assessing renal function.

Glomerular Filtration Rate and Renal Plasma Flow: If a substance is just filtered in the glomeruli and is neither reabsorbed at all nor secreted even to a minimal extent by the renal tubule, its 'clearance' is taken to be equal to the glomerular filtration rate. Inulin, a polysaccharide (of M. W. 5200 and similar to starch but unlike it, is made up of a number -32- of fructose units), is a substance that escapes into the Bowman's capsule and is neither reabsorbed nor secreted. Its clearance has been determined and has a value of about 125 cc. Hence, the glomerular filtration rate is taken to be the same viz — 125 cc/min. Creatinine and sodium ferrocyanide also have similar clearance values and hence, may be disposed off by the kidney solely by filtration, like inulin.

Para-amino hippuric acid (PAH), when present in plasma in very low concentration, is secreted by the tubular epithelium in relatively large amounts. It has been estimated that 0.912 (extraction fraction) of this substance in plasma is cleared when blood flows in the vessels of the nephron. Thus, if the actual plasma clearance is determined (like the clearance for any other substance), the plasma flow rate can be derived. A standard value for PAH clearance is 585 cc. Therefore, the plasma flow will be:— $585 \div 0.912 = 650$ cc. per minute. Blood flow to both the kidneys will be $650 \times 100 \div 55$ (assuming haematocrit value to be 55 vols%) = 1182 cc/min. The clearance of diodrast which is a X-ray contrast medium, is also used for calculating the plasma flow rate. Its extraction fraction is about 0.85 and hence is less than that of PAH. On this account, there is a likelihood of a greater error in the estimation of the plasma flow. Hence, PAH clearance value is preferred to that of diodrast for estimating plasma flow rate. From the glomerular filtration rate and the plasma flow, the filtration fraction can be calculated. It is obtained by dividing 125 (plasma flow) by 650 (filtration rate). Thus, the filtration fraction is $125/650 = 1/5$ (approx.)

Special Procedures employed in investigations into renal functions: Two special techniques were derived in the elucidation of renal function. The brilliant conclusions of Ludwig, Bowman, Heidenhain and others would have remained as mere conjectures, but for these. Richards, by a micropuncture of the Bowman's capsule in the frog (glomeruli easily accessible, being superficial), was able to collect tiny samples of the glomerular filtrate to analyse which, equally precise microanalytical chemical methods were developed. Later, even the Bowman's capsule of the mammalian kidney was subjected to this rather delicate procedure. The chemical characteristics of the filtrate showed irrefutably that filtration was the first step in the formation of urine. Attempts have been made to obtain minute samples of tubular fluid by micropuncture. Only the deepest parts of the loop of Henle were very difficult to get at.

The other advance is by means of the stop-flow technique, as developed by Malvin, Wilde and Sullivan. Preliminarily, an osmotic diuretic (see further on, about these agents). for eg. —

mannitol, is given to promote urine flow in the tubule. Thus, glomerular filtrate is made to pass through the entire tubule rapidly without undergoing any change as regards the concentration of any one of its constituents. Now, the ureter is obstructed and the urine flow stopped. Because of the building up of back pressure in the tubules and thereby raising of the capsular pressure, glomerular filtration ceases. The ureteral blocking is maintained for about 8 minutes, during which time the fluid in the tubule undergoes changes in the composition, depending on the part of the tubule in which it stagnates. Two minutes before the obstruction is removed, inulin is administered by vein. On removal of the obstruction, about thirty successive samples, each of 0.5 cc, are withdrawn from the renal pelvis. The earlier samples are taken to be the fluid which came into a steady state (of composition) in the collecting tubules. The subsequent samples are considered to be from the higher and higher (nearer and nearer the Bowman's capsule) tubular segments. Each sample, which is assumed to have stagnated (during obstruction to flow) in a particular part of the tubule, reflects the function of that part—viz—reabsorption or secretion of particular substances. The sampling is stopped when inulin appears in the samples, showing that glomerular filtration has resumed after the removal of the block. The injection of para-amino hippurate (PAH) during the period of block, brings about the entry of the substance into the tubular fluid, as shown by its presence in the samples. Since filtration did not occur in this period, the presence of PAH is taken to be due to active secretion by the tubular epithelium. This procedure avoids the technical difficulties of the micropuncture studies and hence it has been called a poor man's micropuncture.

RENAL FUNCTION TESTS

In diseases of the kidney, the organ may not be able to excrete urea, uric acid and creatinine, the common waste products found in the urine, with the result that these may be expected to accumulate in blood. But one cannot wait for such a rise in the blood concentration of these substances to occur in order to recognise kidney disease, because such a change in the blood content occurs only in very serious renal impairment. Minor

degrees of renal insufficiency need other tests to reveal them. There are a large number of tests described for this purpose. Only a few, based on water and urea excretion which have a readily identifiable physiological basis, are described here. One of the earliest signs of renal disease is polyuria, though how exactly it is brought about has not been understood. The normal proportion of 2 : 1, between the urine outputs of day and the night is also disturbed, the latter becoming more in relation to the former.

The following are the tests:

Specific gravity determination: In the evening of the day prior to the day of test, a meal rich in protein along with about 200 cc (not to exceed this) of water is given. Further fluid intake is not allowed after this. The urine passed during the night (after the meal) is discarded. In the morning at 8 A. M., 9 A. M. and 10 A. M. urine is collected and the three samples numbered I, II and III, in order. The specific gravity of each sample is measured.

At least in one of the specimens, the specific gravity should be above 1022. In normal subjects, much higher values (even above 1030) are observed. If renal function is impaired, none of the specimens will approach 1022 in value. As the renal condition worsens, the value in every one of the specimens approaches 1010. This test is useful to detect renal inefficiency even when blood urea is within normal range and gives an idea of the concentrating power of the kidney.

Dilution Test: This tests the diluting ability of the kidney. No water is taken after the midnight before the morning of the test. At 7 A. M., the next morning, the bladder is emptied and about 1200 cc of water drunk in as short a time as possible (within 30 min.). Four one-hourly samples at 8, 9, 10 and 11 A. M. are obtained, each time emptying out the bladder. The volume and specific gravity of each sample is noted. In normal subjects, all the water drunk at 7 A. M. would be eliminated by 11 A. M. and at least one sample would have a specific gravity below 1003. In renal disease, this low value is not attained at all, and the amount of water taken at 7 A. M. is not lost within the duration of the test (4 hours).

Fixation of Specific gravity: The specific gravity of urine in advanced renal disease, is fixed around 1010 without any possibility of variation either below or above it, whereas the physiological range is between 1000 and 1040. At this stage, other prominent signs like very high blood urea levels will also be seen.

Urea Concentration Test of Maclean: Food and water are completely denied to the subject for 12 hours (during night) before the test. At 7 A. M. in the morning, the bladder is emptied out and 15 gms of urea dissolved in 100 cc of water, and suitably flavoured, is given. The bladder is emptied at 8, 9 and 10 A.M. The volume of each sample is measured and the amount of urea in each determined. The urea concentration should reach 2.5% in at least one specimen. If the highest value of urea content is below 2.0%, it is taken to be diagnostic of renal impairment. In severe renal disease, the values may be less than 1.0%. The volume of the specimens is also important and it should not exceed 120 ml in any of the three. Urea content of the samples is determined by the hypobromite method.

Urea Clearance Test: This owes its inception to Van Slyke. Reference has already been made to the concept of clearance (see above).

A standard value of urea clearance, for comparison purposes, was obtained by determining it in a large number of normal people and it was found to be 75 cc/minute, with the rate of urine formation (V) being 2 cc/min. Urea clearance fell when the urine flow rate (V) decreased below 2 cc/min, the urea clearance being 54 cc/minute when the rate of formation of urine was 1 cc/min. For values of V between 0.5 cc and 2.0 cc, urea clearance is given by $54\sqrt{V}$. Hence, for all values of V above

2 cc, urea clearance = $\frac{UV}{B}$ (see above). For values of V below

2 cc, urea clearance = $\frac{U\sqrt{V}}{B}$. Maximum clearance expresses the observed clearance as a percentage of the average normal (75 cc).

Thus, maximum clearance = $\frac{UV}{B} \times \frac{1}{75} \times 100 = 1.33 \frac{UV}{B}$

For values of V less than 2 cc, Van Slyke used the term standard Urea Clearance, since this was calculated with reference to a standard value, viz — 54 cc/min. when $V = 1$.

$$\text{Standard Urea Clearance} = \frac{U\sqrt{V}}{B} \times \frac{1}{54} \times \frac{100}{1} = \frac{1.85 U\sqrt{V}}{B}$$

After the usual morning meal (breakfast), the subject is given a cup of water to drink (the time is noted) and the bladder is emptied out and the specimen discarded. After an hour, urine is voided completely (specimen I). Urine is again collected (completely emptying the bladder) an hour later (specimen II). After the first specimen has been obtained, a few ccs of blood are drawn and the blood urea content is determined (B). The urea contents of the two specimens are then determined. The two urine samples should show agreement within 10 %. Otherwise the test is vitiated and will have to be repeated. The formula (Maximum Clearance or Standard Clearance) to be used in the case of either specimen will depend on whether V is more or less than 2 cc/min. The calculated values should show close agreement, if procedural errors have been avoided. In the case of children, allowance will have to be made for the difference in body surface area. V should be modified by the factor $A/1.73$, wherein A — body surface of the child in sq. M. and 1.73 — assumed to be the average value for adults. Thus, in the place of V , $\frac{V \cdot A}{1.73}$ has to be used in the calculation. For very tall or very short adults also, correction should be made. Charts have been prepared giving the correction factor straightaway.

A modification of the urea clearance method is to give 15 gms of urea as a preliminary to the test, with the idea that it will promote diuresis and so enable collection of more accurate specimens. But this contention is nullified by the fact that water given in the test also provokes diuresis. The modified test, however, may be employed when the subject is habitually on a low protein diet.

In interpreting the results, the normal urea clearance is taken to be in the range 100 ± 30 per cent of the average

normal. Values less than 70% of the normal average are indicative of renal damage. Sometimes, even with blood urea remaining within normal limits, the test may show a fall in urea clearance to about 50 % of the normal. In uraemic coma, very low values (below 5 %) are seen.

Phenolsulphonphthalein Test: Substances of extraneous origin are eliminated from the blood by the kidney. 10 or 15 minutes after the subject drinks a cup of water, the urine is completely voided. A very small quantity (6 mg) of phenol red dissolved in 1 cc of water is given intramuscularly. An hour and ten minutes later (10 min. allowed for dye to mix thoroughly in blood), the bladder is emptied (specimen I) and a second specimen of urine obtained after another hour. The phenol red content in both samples is determined. Normally, 40-60 % of the 6 mg is excreted in the first hour and 15-25 % in the second hour and thus, 60-80 % of the dye given is got rid of in two hours. Fall in the amounts of dye lost in the two samples, is strongly suggestive of renal impairment.

Other Tests: The blood concentration of serum albumin and globulin also will reveal abnormalities in renal function.

Inulin clearance, PAH clearance and Diodrast clearance tests are also useful (see above).

The surgeon employs two procedures — 1) intravenous pyelography — noting the earliest time of arrival of a dye along the ureter in the bladder by means of cystoscopy. 2) X-rays of the kidney outline are taken after administering contrast media.

Renal function tests serve another purpose — namely — in kidney transplant surgery. The donor's kidneys are investigated before he is permitted to part with one kidney to the recipient.

Removal of one kidney is quite compatible with normal life, provided the remaining kidney, which hypertrophies (increases in size), remains healthy. With a loss of upto $\frac{2}{3}$ rds of kidney substance, individuals can carry on reasonably well, though mean

clearances are at the lowest value of normal. Loss of $\frac{3}{4}$ ths or more leads to renal failure with retention of nitrogenous substances and uraemia.

RENAL REGULATION OF ACID-BASE BALANCE

In addition to carbonic acid which is eliminated by the lungs as carbon dioxide, other non-volatile acids such as lactic, pyruvic acids, β -hydroxy butyric acid, aceto-acetic acid, citric acid and inorganic acids like hydrochloric, phosphoric and sulphuric acids are produced constantly on account of metabolic reactions. These acids are effectively buffered at the expense, however, of a decrease in HCO_3^- which is the chief component of the buffer base available for this purpose. Acids added to the extracellular fluid react chiefly with HCO_3^- to yield carbonic acid and a salt of the acid. The carbonic acid, in turn, yields CO_2 which is excreted via the lungs. Thus, a strong acid is converted into a weak acid.



The result is that for each molecule of HA added, one molecule of sodium bicarbonate disappears from the plasma. Production of these non-volatile acids normally exceeds the intake of available neutralising substances by about 50 to 100 m. eq. The alkali reserve (bicarbonate content of plasma) would be exhausted if the increment in fixed acid anions, temporarily replacing HCO_3^- anions, were not removed from the body and HCO_3^- restored. This is done by the kidneys, the ultimate regulator of acid-base balance. It functions in two ways —

- 1) by excreting the actual H^+ which would alter the pH of blood, if not eliminated in urine.
- 2) by the reabsorption of HCO_3^- as sodium bicarbonate and maintaining the alkali reserve.

The glomerular fluid contains $\text{NaHCO}_3/\text{H}_2\text{CO}_3$ and $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ buffer systems. These facilitate the excretion of H ions. The normal urinary pH is about 6. The difference

in titrable acidity between the pH of the urine and that of plasma (7.4) represents the amount of acid removed from the plasma by the renal mechanisms. The pH of urine varies from 4.5 to 8.2 according as the kidney removes excess acid or excess base. Acidification of the urine is accomplished by exchange of intracellular H^+ ions for intraluminal cations, principally Na^+ (ion exchange mechanism). Mobilisation of H^+ ions for tubular secretion is associated with ionization of carbonic acid, which is formed from metabolic CO_2 and water. In the proximal tubule, the exchange of hydrogen ion proceeds first against NaHCO_3 . The tubular cells are rich in carbonic anhydrase which catalyses the formation of H_2CO_3 . (Fig 26) This carbonic acid dissociates into H^+ and HCO_3^- . The HCO_3^- combines with H^+ to form H_2CO_3 , which decomposes into $\text{H}_2\text{O} + \text{CO}_2$, because of low PCO_2 in the

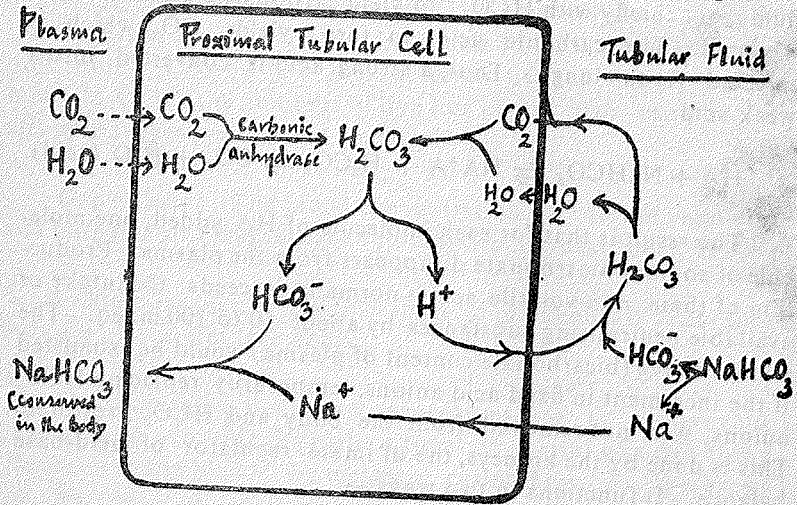


Fig. 26

tubular fluid. CO_2 is reabsorbed and dissolves in tubular water to give H_2CO_3 again. Na^+ is reabsorbed along with HCO_3^- in the tubular cells. Thus, NaHCO_3 returns to the plasma. For one ion of Na^+ reabsorbed, one H^+ ion is excreted. Tubular cells also contain K^+ which also is excreted in exchange for Na^+ - i.e. -

H^+ and K^+ both compete with each other for exchange with sodium. This is influenced by aldosterone. When the plasma bicarbonate level is normal, about half of that filtered is reabsorbed in the proximal tubule and the remainder in the distal tubule. After all the HCO_3^- has been reabsorbed, H^+ ion secretion then is used to deal with Na_2HPO_4 . (Fig. 27) In this mechanism, the exchange of a sodium ion for a secreted H^+ ion, changes Na_2HPO_4 to NaH_2PO_4 .

The third mechanism for the elimination of H^+ ion is the production of ammonia in the distal renal tubules. (Fig. 28) De-amination of the amino acid, glutamine by glutaminase gives rise to ammonia. This reacts with H^+ ion to form ammonium ions which combines with chloride of NaCl in the glomerular filtrate to form NH_4Cl . The sodium enters the tubular cell to combine with HCO_3^- and is reabsorbed as $NaHCO_3$. Under normal conditions, 30 to 50 m eq. of H^+ ions are secreted per day as NH_4 ions. This mechanism is important because the enzyme glutaminase is sensitive to pH changes. When the intracellular pH is low, excretion of NH_4 ion is increased, as glutaminase activity is increased. Normally, 30 to 50 m. eq of ammonia are excreted daily. When the blood pH falls, the urinary NH_3 increases upto even ten-fold, depending upon the severity of the acidosis.

The Alkaline Tide of Urine :

- 1) Morning tide — Morning urine, shortly after rising, is less acidic than that formed during sleep. Morning alkaline tide was attributed to increased pulmonary ventilation after rising (movements etc.), but is probably associated in some unexplained way with respiratory changes incident to the return of consciousness.
- 2) Post-prandial alkaline tide — Alkaline tide occurs within an hour after a meal. Probably it is connected with drowsiness and reduction of pulmonary ventilation after a meal and not likely to be due to loss of HCl in gastric juice, for, pancreatic secretion follows immediately.

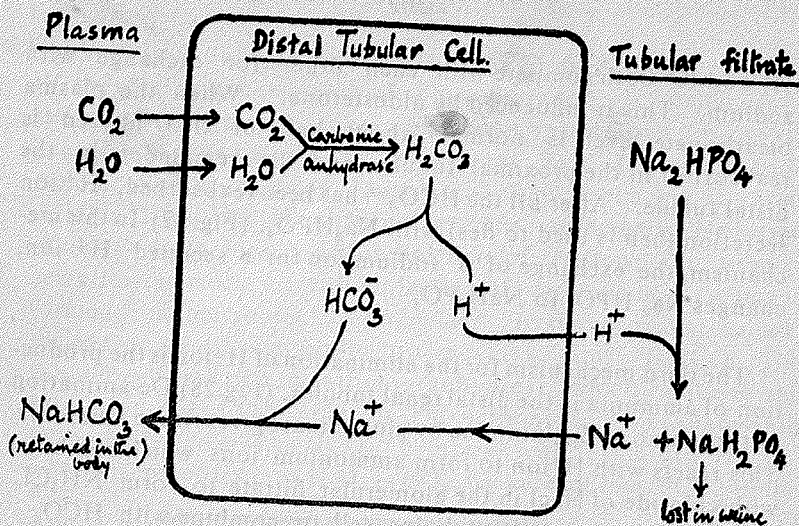


Fig 27

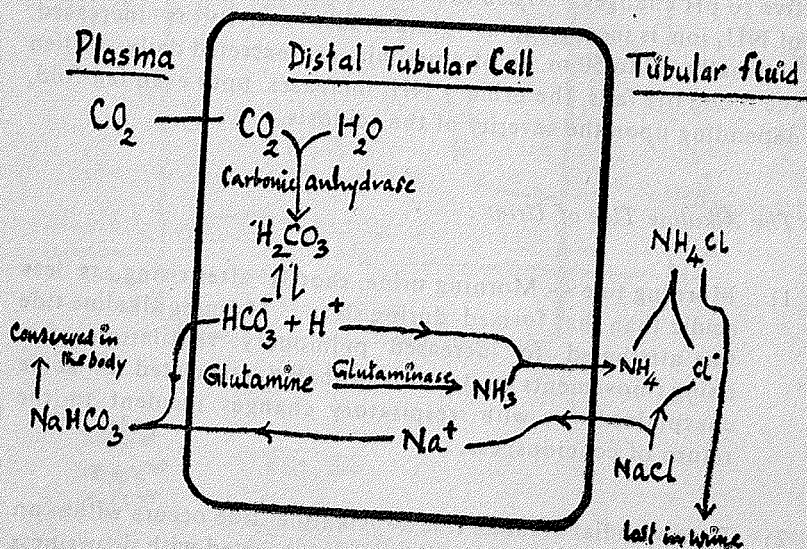


Fig. 28

CONDITIONS ALTERING URINE FORMATION — WATER BALANCE

- 1) **Water Intake:** When large quantities of water (1-2 litres) are drunk, especially on an empty stomach, diuresis (increased urine output) starts after a latent period of 15-30 min., becomes maximum in the second hour, when output may be as high as 1300 cc/hr. (resting 50 cc/hour.) Then it declines and returns to normal in about 3 to 4 hrs. when all water drunk is eliminated. Even 5 litres drunk in about 2 hrs. is eliminated within 4-5 hrs.)

The specific gravity of urine is low — 1.000 to 1.002. The concentration of NaCl and urea is very low, though total quantity of these substances excreted may be raised slightly (compensated for, by reduced excretion after diuresis). The total solid loss is not significantly raised and the effect is mainly on water excretion.

After drinking water, electrolytes diffuse out from the intestinal wall into the water in the lumen of the gut. As the osmotic pressure approaches that of plasma, the solution is absorbed into the blood, leading to a slight increase in plasma volume and slight reduction in crystalloid and colloid osmotic pressure. But there is no increase in glomerular pressure or alteration in the osmotic pressure — i. e., — the diuresis is not due to changes in effective filtration pressure. Glomerular filtration is not increased (unless volume of urine exceeds 900 cc/hr). Inulin and diodrast clearances are normal, showing that diuresis of water drinking is due to diminished tubular reabsorption. The effects produced by water intake is not due to a direct action on the kidney, but through the hypophysis by affecting ADH release.

The diuresis of water drinking is similar to that seen in diabetes insipidus (Physiological Diabetes Insipidus of Verney) and is probably due to temporary inhibition of the ADH secretion reflexly from the osmoreceptors. The delay in the onset of diuresis is not due to the time taken for plasma to be diluted by water absorbed from the intestines. Even after water is injected into the veins directly, there is a time lag before diuresis begins.

Injection of posterior pituitary extract inhibits water diuresis. Injection of hypertonic saline in the internal carotid artery inhibits water diuresis.

- 2) **Water deprivation:** In man, after complete water deprivation for 4 days, with an otherwise adequate diet, renal circulation is unchanged. No decrease in plasma flow and no haemoconcentration occurs because fluid is drawn from tissue spaces. Glomerular filtrate volume is reduced by 20% and urine volume to 30-40 cc/hr. For an urinary output of 30 cc/hr, urea, creatinine, phosphate and other nitrogenous and non-nitrogenous solids become concentrated to the maximum extent and unless urine volume is increased, these substances cannot be eliminated in larger amounts. (Further reduction in urine volume diminishes excretion of solids which accumulate in blood, leading on to uraemia).

Water deprivation in infants is more serious, for, the kidney is probably not fully developed functionally and the urine is hypotonic - i.e. - more water is required to eliminate a given amount of solid. The glomerular filtration rate is also low. Hence, a small loss of fluid, as in diarrhoea and vomiting, may lead to greater retention of nitrogenous constituents.

Effects of water deprivation (dehydration): 1) loss of body weight 2) disturbance of acid-base equilibrium, especially towards acid side. 3) Rise in non-protein nitrogen in blood. 4) Rise in concentration of plasma protein and chloride (haemoconcentration). 5) Rise in temperature, pulse rate and cardiac output. 6) Thirst, dryness of mouth, wrinkling and looseness of skin.

- 3) **Drinking Saline Solutions:** Isotonic solution — No significant diuresis occurs when isotonic saline is drunk, the extra fluid is only eliminated slowly. With 1-2 litres saline, no diuresis takes place for next 6-8 hrs. Excess of water and salt is excreted during the next few days. If about 3 litres are drunk in an hour, a moderate degree of diuresis occurs (300 cc/hr) and output of urine remains above normal level (60 cc/hr.) for 24 hrs.

Isotonic KCl (1.3 %), if taken orally, is rapidly excreted like urea, leading to diuresis.

(Saline is retained for many hours when given by mouth or rectum, but is more rapidly eliminated if introduced directly into circulation).

- 4) Intravenous saline injections: With a large intravenous infusion of normal saline, diuresis starts after a brief latent period of a few minutes, reaches its maximum in 2 hours and gradually declines. The effect is mainly due to decreased tubular reabsorption. No decrease in plasma crystalloid osmotic pressure occurs, but dilution of plasma proteins and consequent fall of colloid osmotic pressure may increase glomerular filtration.

Intravenous injection of hypertonic saline solution causes diuresis. Fluid is drawn from tissues into the blood. A rise in blood volume, blood pressure and renal blood flow together increase glomerular filtration.

- 5) Ingestion of salts: a) After ingestion of 1 oz NaCl, flow of urine is increased to 1200 cc/hr. The rate of excretion of salt is comparatively slower. More water is drunk due to thirst induced by salt. The salt concentration is reduced and the excess fluid and salts are slowly eliminated in the course of a few days.
- b) Salt deprivation — Diminished excretion of Na^+ and Cl^- in urine, results. Reabsorption of Na^+ and Cl^- in tubule is practically complete. Blood pressure is unchanged, but glomerular filtrate is decreased by 30% and urea clearance is also decreased. Urea retention in plasma of 30–80 mg% occurs. Decrease in plasma volume but with increase in colloid osmotic pressure of plasma occurs. Diuretic response to drinking of water is not so striking.
- 6) Exercise: Urine volume and Cl^- excretion are reduced. Maximum decrease is at about 15 min. after start of exercise and full recovery within $1\frac{1}{2}$ hours after vigorous exercise.

This is due to the hypothalamico-hypophyseal mechanism increasing secretion of ADH and reducing urine volume. Other factors are — Increased retention of water in active muscles, visceral vasoconstriction, loss of water by sweating and reduced glomerular filtration resulting from afferent arteriolar constriction.

- 7) Emotions: Urine volume is reduced (but sometimes increased). Action is through hypothalamico-hypophyseal mechanism and thereby on ADH release.

Outpouring of adrenaline from the suprarenal medulla may be a contributory factor in the reduction of urine volume.

Emotions may cause modifications of micturition reflexes, leading to frequency of micturition (without increase in volume),

DIURETICS

Substances which increase urine formation are called diuretics eg. — caffeine, Na_2SO_4 , urea, saline solutions, acidifying salts like NH_4Cl , mercurial salts and under certain circumstances, digitalis.

- 1) Some substances act by dilution of blood and increasing glomerular filtration (dilution diuresis) eg. — Intravenous injections of hyper tonic saline, glucose etc.
- 2) Others act by reducing tubular reabsorption (tubular diuretics) — eg. — Na_2SO_4 , Urea, NH_4 salts by increasing osmotic pressure of fluid within the lumen. Mercurial diuretics act by depressing tubular epithelial cells. Phloridzin paralysis— tubular function (glucose in hyperglycemia causes diuresis by increase in osmotic pressure of tubular fluid).

Caffeine acts partly by depressing tubular absorption and partly by renal vasodilatation and increase in number of patent capillaries.

Digitalis, normally, has no action, but in cardiac oedema causes marked diuresis by improving the failing circulation.

Action of alcohol is similar to that of water.

HORMONES INFLUENCING RENAL FUNCTION

A number of hormones affect reabsorption of specific substances in renal tubules.

- 1) Adrenal cortical hormones, mainly aldosterone, increase the reabsorption of Na^+ and Cl^- and decrease the reabsorption of potassium (i. e. — these hormones reduce the excretion of Na^+ and Cl^- and increase excretion of K^+ in urine).
- 2) The anti-diuretic hormone of the neurohypophysis increases the reabsorption of water, and it controls the proportion of water which is reabsorbed in the distal segment. The water reabsorbed from the proximal segment is not under pituitary or other hormonal influence.

Suppression of the anti-diuretic hormone release due to hypothalamohypophysial lesions, results in polyurea (diabetes insipidus), when urinary excretion is 4 to 10 litres or even upto 30 litres in maximally severe cases.

- 3) The anti-diuretic hormone diminishes the reabsorption of Na^+ and Cl^- from the proximal tubule.
- 4) The Pars Distalis seems to increase renal elimination of water (through thyrotropic and adrenocorticotropic hormones). The polyurea of neurohypophysial lesion is diminished by thyroidectomy and increased by thyroid extract.

The Pars distalis has a diuretic action opposing the action of neurohypophysis. (Removal of Pars Distalis is followed by decrease in renal circulation and inulin and diodrast clearances).

- 5) Parathyroid hormone is said to decrease reabsorption of phosphate, increasing its excretion in urine (by lowering the renal threshold for phosphate).

ABNORMAL CONSTITUENTS OF URINE

Albumin, casts, blood cells, pus cells, blood, RBCs, haemoglobin, bile salts and bile pigments, glucose etc.

Abnormalities in urine may be due to kidney dysfunction or due to extra-renal lesions

Among diseases affecting kidney mainly are—

- 1) Glomerulo-nephritis: (inflammatory condition.) Glomeruli and tubules are affected.
- 2) Nephrosis: degeneration process. Tubules are affected.
- 3) Arteriosclerotic kidney — sclerosis of vessels is the cause.

Some of the manifestations of kidney disease are:

- 1) Oliguria 2) Albuminuria 3) Various types of casts
- 4) Oedema 5) Reduced ammonia output 6) acidosis
- 7) Hypertension, cardiac hypertrophy, retinal changes
- 8) Polyuria, nycturia 9) Lipaemia, hypercholesterolaemia
- 10) Uraemia (terminal).

Oedema is due to excessive accumulation of fluid in tissues, owing to lowered colloidal osmotic pressure in plasma and chloride retention in kidney. In the nephritic condition, usually, there is no glycosuria.

Functional albuminuria: A transient albuminuria occurs due to temporary functional change in glomerular membrane, in response to stresses like prolonged exposure to cold (which causes vasoconstriction) and after violent exercise when considerable oxygen debt is incurred.

Orthostatic or postural albuminuria is a variant of functional albuminuria. Albumin is passed in the urine only in the upright position. On lying down, albuminuria ceases. More common in juveniles at the age of puberty (juveniles who display excessive lordosis). Condition clears with advancing age.

Glycosuria: Endocrine, nervous, alimentary, renal, phloridzin, emotional etc.

Renal Glycosuria: Sugar appears in urine at normal or slightly elevated plasma glucose level. It occurs in a person whose renal 'threshold' for glucose is low. The filtration rate and renal plasma flow are generally normal, but the glucose Tm (375 mgm) is reduced. The condition is not considered to be pathognomonic.

The renal threshold for glucose varies considerably. Though, the amount of glucose filtered is the same, the ability of the tubules to reabsorb varies.

The 'threshold' level tends to rise with age and in arteriosclerotic patients in whom blood sugar may rise to 200-240 mgm% and still may not be excreted in urine.

RENIN

The juxtaglomerular cells in the afferent arteriole (Fig. 24) are thought to be the source of renin, an enzyme which is present in the form of granules in these cells. The number of granules increases or decreases according to the blood pressure. The release of renin into the blood stream was originally held by Goldblatt to be due to renal ischaemia, as caused by narrowing of the renal artery. But the exact stimulus has yet to be identified. According to one view, changes in the transmural pressures in the kidney excite certain baroreceptors which probably are the same as the juxtaglomerular cells.

Renin acts on a plasma globulin, namely angiotensinogen—converting it into angiotensin I, a decapeptide. This is further converted to angiotensin II which is made up of 8 amino acid residues. The last mentioned product is a very powerful pressor substance and perhaps the most powerful of all known to medicine. Renin itself has no action with regard to the elevation of blood pressure. The exact physiological role of renin — angiotensin mechanism cannot be pin-pointed with any certainty. All that can be said now is that it may be responsible for maintaining adequate blood flow to the kidney when blood supply to the kidney tends to be diminished. The physiological or pharma-

cological effect of renin administration is to elevate the blood pressure. So, as a corollary, in the intact animal, elevated blood pressure will ensure adequate blood supply to the kidney so necessary for its function.

Renin is also involved in the control of secretion of aldosterone (see adrenal cortex). By effecting the release of aldosterone from the adrenal cortex, it helps to maintain renal blood flow, indirectly. Retention of water is due to the sodium conserving action of aldosterone and consequently the blood volume itself is augmented, thereby raising the blood pressure.

Goldblatt experimentally produced acute hypertension by clamping the renal artery. This temporary phase of hypertension is due to the renin-angiotensin mechanism. But in longstanding cases of raised blood pressure, a humoral agent like renin has not been detected in the blood stream. It is possible that substances antagonistic to renin may be produced in these cases. In unilateral renal ischaemia, as produced by Goldblatt, permanent elevation of the blood pressure does not occur as long as the normal kidney is present. Removal of the normal kidney produces permanent hypertension. In the juxtaglomerular cells themselves, there seem to be present anti renin substances. Further, there is an enzyme, angiotensinase, which probably may be elaborated by the normal kidney. It has been found recently that there is yet another hypertensive agent in the renal tissue known as sustained pressor substance. The functional relationship between this agent and renin is not yet known. To complicate matters, ferritin, also known as vasoexcitatory material (VEM), has been found to be liberated by ischaemic renal tissue. There is also another substance designated as vasodepressor material (VDM) of hepatic origin. The inter-relationship among all the substances mentioned is awaiting clarification.

PHYSIOLOGY OF MICTURITION

Urine formed in the kidney passes into the renal calyces and the pelvis of the kidney and descends along the ureter to the

bladder, where it accumulates to be emptied periodically. The emptying of the bladder and the evacuation of urine to the exterior is called micturition.

Anatomy: The ureter is a narrow tube (diameter 3—4 mm), one on either side and about 25 cms long. It leaves the kidney at the hilus and passes down into the pelvic cavity. The ureters penetrate the bladder obliquely, opening into its cavity. The last 2 cms of the lower end of the ureter is embedded in the bladder muscle. Terminally, the ureter is anchored to the bladder by the fusion of its inner layer with the mucosa of the bladder as well as the continuity of its muscle fibres with those of the bladder. The bladder wall around the intra-vesicular part of the ureter can slide up the ureter when the bladder fills with urine. There is no sphincter at the lower end of the ureter. All the same, urine cannot get back into the ureter from the bladder, on account of the structural peculiarities of this region. The uretero-vesicular opening is patent only when urine trickles down at intervals. It closes when fluid in the bladder attempts to enter the ureter, as would happen during micturition when intra-vesicular pressure rises steeply.

The urinary bladder is a bag-like structure situated in the pelvic cavity. It stores urine and discharges it at intervals.

The urethra is a passage leading out of the bladder and opens to the exterior.

The urethral orifice is situated at the most dependent part of the bladder and is guarded by what is known as the vesicular sphincter (internal sphincter). The triangular area marked out by the urethral orifice and the two ureteral orifices is called the "Trigone". The muscle of the bladder wall is referred to as the detrussor urinae. The trigone being derived embryologically from the mesonephric duct, is separated anatomically from the detrussor. It may not have any role in micturition and at the most may help to close the internal urethral opening during ejaculation of semen.

The external sphincter, composed of striated muscle, encloses the membranous portion of the male urethra and the proximal part of the female urethra.

The bulbo-cavernosus muscle is applied to the urethral bulb and surrounds the corpora cavernosa penis. It also exerts a constrictor action upon the urethra, in the male.

Histology: The ureter has the following structure—from within outwards.

1. Mucous membrane lined by transitional epithelium (basement membrane absent for transitional epithelium)
2. Muscle coat (plain muscle) outer circular and inner longitudinal
3. Outer adventitia of connective tissue.

The urinary passages from the top of the ureter downwards upto the internal sphincter of the bladder are lined on the inside by transitional epithelium several layers thick. This rests on a fibro-elastic lamina. The cells of the epithelium, it is said, can slide one over the others, in order to permit expansion of the walls when distended with urine. In the empty state, the epithelium presents deep folds which flatten out when the passages are filled with urine. Though, formerly, the muscle fibres in the middle layer, especially of the ureter and the bladder, were thought to be disposed in the three layers, their direction being considered as longitudinal, circular and again longitudinal from within outwards, it is now felt that they are arranged in the form of two sets of spirals, each interlacing with the other at different angles in different parts of the urinary tract. In the upper reaches of the ureters, the muscle fibres have interconnecting bridges to form, as it were, a syncytium with a functional continuity.

Urinary bladder has the following structure:—

- a) Mucous membrane formed by transitional epithelium; covers the inside of the bladder. (It contains alkaline phosphatase)
- b) Muscular wall – 3 layers
 - Outer fibres – longitudinal
 - middle-circular (oblique and transverse)
 - inner – longitudinal reticular pattern.

Though formerly, three separate layers of muscle fibres (longitudinal, oblique and transverse and longitudinal-innermost) were described in the middle layer, now it is felt that the whole of the muscular wall of the bladder is made up of decussating muscle fibres running in different directions. A recent view is that there is no internal sphincter which is only a tubular structure formed by the detrussor fibres continuing into the prostatic urethra in the male, and the whole of the urethra in the female.

Urethra : a) Male — The urethra is lined in prostatic part by stratified epithelium, but elsewhere by stratified columnar, except near the orifice where stratified squamous type is seen.

b) Female — It is lined throughout by stratified columnar epithelium except near the bladder where transitional epithelium replaces it.

The capacity of the human bladder is about 400 cc (350—450 cc).

INNERVATION OF URINARY TRACT

Ureters

Sympathetic { Upper part — from renal plexus
Middle part — spermatic or ovarian plexus
Lower part — hypogastric nerves

Action of sympathetic fibres is predominantly motor (inhibitory fibres are also present).

Parasympathetic — Probably present, but not anatomically demonstrated (parasympathomimetic drugs cause motor effects).

Innervation of urinary bladder : The muscles of the bladder wall and internal sphincter (plain muscle) have a double innervation. 1) Sympathetic fibres are given off from the hypogastric nerves (hypogastric plexus in man) and 2) Parasympathetic fibres are derived from the pelvic nerves (nervi erigentis).

1) Sympathetic fibres:— These arise from the lateral horn cells of the 2nd or 3rd to 5th lumbar segments of spinal cord. They pass through the inferior mesenteric plexus, presacral nerve (superior hypogastric plexus) and the inferior hypogastric plexus to end in the hypogastric ganglion which is situated one on each side of the rectum. Postganglionic fibres are given off from here to form the vesical plexus supplying the bladder.

The sympathetic nerves have been held to be inhibitory to the detrussor muscle and motor to the trigone, internal sphincter and smooth muscle of the proximal part of the urethra.

Electrical stimulation of the presacral or hypogastric nerves provokes contraction of internal sphincter, constriction of ureteral orifices and increases the tone of trigone. The detrussor muscle is relaxed after a brief initial contraction. These effects favour the filling of the bladder (nerves of filling).

Adrenaline has the same effect as sympathetic stimulation.

2) Parasympathetic fibres:— These arise from the 2nd to 4th sacral segments of the spinal cord. They join the pelvic nerve (nervi erigentis) and end on the ganglion cells lying close to or within the bladder wall from where postganglionic fibres arise to end on the muscle fibres of the bladder.

Parasympathetics are motor to the detrussor and inhibitory to the internal sphincter.

The stimulation of the parasympathetic fibres makes the bladder muscle contract and the internal sphincter relax. Both actions serve to empty the bladder (nerve of emptying).

Acetyl choline has the same effect as parasympathetic excitation.

Both sets of nerves appear to exert a constant influence upon the tone of the detrussor muscle and internal sphincter, the actions being reciprocal.

In this context, it must be stated that doubts are cast now on the significance of dual innervation of the bladder. The view has arisen that sympathetic nerve supply to the bladder has no functional significance in micturition. If at all, these fibres may help to close the internal urethral opening during the sex act.

The external sphincter is innervated through the pudendal nerve, which is derived from the upper 3 sacral nerves (parasympathetic) and from upper lumbar nerves (sympathetic).

The afferent impulses from the bladder travel in both groups of nerves — 1) those concerned with reflex bladder movements mainly are conducted in pelvic nerves (enter spinal cord by dorsal roots of 2 and 3 Segments.)

- 2) Sensations set up by distension, in pelvic and hypogastric nerves.
- 3) Sensation of pain chiefly in hypogastric; but also in pelvic nerves (enter spinal cord in dorsal roots of 1-3 L-Segments.)
- 4) Tactile and thermal sensations and sensation of pressure or filling of bladder mainly in pelvic nerves.

Afferent fibres from the urethra travel in the pudendal nerves. The detrussor muscle of the bladder exhibits two types of activity.

- 1) Tonus (or a sustained contraction which is always present).
- 2) Intermittent contraction — These precede emptying and are slow and weak to begin with becoming stronger and more frequent later.

Both are dependent upon the parasympathetic nerve supply to the detrussor muscle.

Filling of the bladder: Rhythmic contractions of pelvic and ureteral muscles are propagated from the renal pelvis down the ureter in the form of peristaltic waves at the rate of 2-3 cms/sec and frequency of 1-5 min, depending on the volume of urine formed

by the kidney. These waves propel the urine into the bladder and serve to fill it. The urine enters the bladder not in continuous stream but in separate squirts, synchronous with the arrival of the peristaltic waves. The bladder muscle, just like the muscular coat of other hollow viscera, is capable of adjusting its tone and adapting its capacity to changes in volume of its contents with relatively little alteration in the intravesical pressure. This is called postural or adaptation reflex. It is different from the behaviour of a hollow elastic bag of nonliving material (rubber) which shows progressive rise of internal pressure when the volume of its contents is increased.

The postural adaptation reflex in the bladder can be demonstrated by catheterising the bladder and connecting the catheter to a manometer. If fluid is injected into the bladder, 50cc at a time, the injection of the first 400 cc produces only slight and transitory changes in pressure. The first 50 cc cause a slight rise in pressure, followed by a decline to near its previous level, as adaptation occurs. Every subsequent injection (upto 400 cc) causes a transient rise followed by a fall to a little higher than the previous pressure. This proves that the detrusor presents only a momentary tonic resistance to distension and then adapts its tonus to the new volume of the contents. (But the pressure nevertheless rises gradually as fluid is injected into the bladder. A paralysed - denervated - bladder behaves like an elastic bag).

When the contents of the bladder are more than 400 cc, the pressure curve rises more steeply, especially when the volume approaches 600 - 800 cc.

Retention of Urine in the Bladder : Urine is retained in the bladder by the closure of the ureteral meatuses which prevents its returning to the kidney and by tonic contractions of the sphincters which prevent its flowing into the urethra. The sphincters can resist a pressure of 70 - 100 cms of water. This resistance is due to a reflex contraction of the internal sphincter (plain muscle), adapted to the volume of urine in the bladder (postural reflex) and to automatic or voluntary contraction of the external sphincter (striated muscle).

Micturition is a reflex act, but is under voluntary control. In infants (and children), or in cases where, as a result of disease or injury, the bladder is deprived of its connection with higher nerve centres, micturition is purely an involuntary (reflex) act.

Normally, micturition is—

- 1) initiated voluntarily (by effort of will).
- 2) can be voluntarily inhibited.
- 3) can be interrupted at any stage.

Tension is the adequate stimulus for the sensory nerve endings in the bladder wall. As urine accumulates, the bladder gets distended and intravesical pressure rises. When the pressure in the bladder rises to 15 – 18 cm of water, as happens when the contents are about 400 cc, afferent impulses which are set up, travel to the nerve centres and the desire to urinate is felt. It is said that the reflex occurs even at lower vesicular pressures and when contents are 250 – 300 cc (10 cm H₂O), especially if accumulation is rapid. The desire is accompanied by a vague feeling in the penis or perineum. When the desire to micturate is felt, evacuation can be prevented or given effect to, voluntarily. Usually, the desire is restrained until a suitable opportunity for emptying the bladder presents itself. The restraint consists of contraction of the external sphincter and perineal muscles and (inhibition) relaxation of the detrussor (and reciprocal increase in tone of internal sphincter).

When the desire to micturate is complied with, the restraint is removed, the voluntary contraction of the external sphincter is inhibited and a chain of reflexes commences, which results in the emptying of the bladder. (The process can be voluntarily inhibited at any stage by contraction of the external sphincter).

During micturition, the detrussor muscle contracts, the internal and external sphincters are relaxed and the urine is expelled with a considerable force, the intravesical pressure rising upto 130 cms of H₂O.

At the end of micturition, in the male, the bulb-cavernosus muscle (ejaculator urinae) contracts rhythmically (Janet's piston stroke) and the last drops of urine left in the urethra are expelled.

In the female, micturition ends more abruptly.

Micturition is usually preceded by (or started by) a contraction of the abdominal muscles and accompanied by relaxation of perineal muscles and a slight expiratory effort with the glottis closed. These assist micturition, but are not indispensable to it. Abdominal contraction can be sustained throughout the act to accelerate evacuation.

Even when there is no desire to micturate, the act can be initiated voluntarily and a few cc of urine can always be expelled.

The desire to micturate can be voluntarily overcome as long as the bladder contents are less than 700 cc. Beyond this, there is a painful sensation in the hypogastrium and an urgent need to evacuate is felt. When the intravesicular pressure is 100 cms of water, the bladder is evacuated, however strong may be the will to retain the urine.

The reflex mechanism of micturition : Barrington has demonstrated in the cat, existence of six coordinated mechanisms in the act of micturition.

- 1) Contraction of the detrussor muscle is evoked by distension of the bladder (at pressure 10 cm) The afferent and efferent paths of the reflex arc are in the pelvic nerves and the centre is in the hind brain (pons and medulla). Contraction of the detrussor is accompanied by a reciprocal relaxation of the internal sphincter.
- 2) Contraction of the detrussor is provoked by flow of urine through the urethra. Afferent path is pudendal nerve, the efferent, the pelvic nerve and the centre is in the hind brain. But this reflex contraction of the detrussor caused by the first reflex is sustained and it ensures complete evacuation of the bladder once it has commenced.
- 3) Weak, transitory contractions of the detrussor are elicited by distension of the proximal part of the urethra. The afferent and efferent paths are in the hypogastric nerves and the centre is in the sacral part of the spinal cord.

- 4) Relaxation of the external sphincter occurs when urine flows through the urethra. The afferent and efferent paths are in the pudendal nerve and the centre is in the sacral part of the cord.
- 5) The external sphincter relaxes when the bladder muscle contracts. Afferent path is in the pelvic nerve, efferent in the pudendal and centre is in sacral part of spinal cord.
- 6) There is relaxation of the plain muscle in the proximal third of urethra when the bladder is distended. Afferent and efferent paths are in pelvic nerve and centre in sacral part of cord.

In the normal act of micturition, the first reflex viz., contraction of the detrussor provoked by distension of bladder, brings on all the reflexes, in order (except the 3rd), automatically into action. The 3rd reflex is probably not significant normally. Though these reflexes have been shown to occur only in the cat, there is no reason as such to suppose that these may not feature in human micturition. There is, however, no information regarding the ability of the cat to either voluntarily stop micturition or bring it about at will. The human subject can do both.

Centres for micturition : These are situated in the spinal cord, brain stem, cerebral cortex and hypothalamus.

Spinal centres lie in 2nd, 3rd and 4th sacral segments (also another spinal centre in 4th to 6th lumbar segment). Sacral cord has the spinal centre for 3rd to 6th Barrington reflexes. The brain stem centre was thought to extend from the middle of the motor nucleus of 5th nerve to rostral end of hind brain. Bilateral destruction of the centre suppresses normal evacuation of bladder. It is now questioned whether the exact location of the brain stem centre can be delineated in man. It may probably be situated in the pons. It has both facilitatory and inhibitory effects on the spinal centre. This centre seems to bring about continuation of the detrussor action along with the relaxation of the external urethral sphincter in order that the bladder is completely emptied. Otherwise, because of the cessation of impulses from the bladder, micturition may come to a stop before the bladder is emptied.

Centres in the cerebral cortex in motor area (extreme top end and paracentral lobule) exert 'voluntary' control over bladder function. Electric stimulation of premotor area causes rise in vesical pressure. A similar effect from upper part of post-central gyrus is observed. Motor fibres travel in pyramidal tracts. In infants, tracts are not myelinated and so there is no voluntary control. Stimulation of anterior nuclei of hypothalamus increases the tone of the bladder, while stimulation of posterior nuclei causes inhibition of tone. The paracentral lobule receives impulses from the bladder which are concerned with intravesicular sensations like pain of spasm.

Micturition is a function of the autonomic nerves but is under the control of cerebral cortex.

Effect of nerve section and cord injuries on micturition :

- 1) Section of hypogastric nerves—This does not affect micturition, for, these nerves do not contain afferent or efferent fibres essential for micturition and though this nerve supplies motor fibres to internal sphincter, the external sphincter alone can prevent escape of urine and incontinence does not occur.
- 2) Section of pudendal nerve alone has also not much effect on micturition though external sphincter is paralysed.
- 3) Section of posterior sacral roots interrupts the afferent pathways (pelvic and pudendal nerves). Bladder wall becomes flaccid and resistance of internal sphincter is increased. Over-distension with overflow incontinence occurs. Sensations, except those of pain, and over-distension are lost.
- 4) Section of sacral nerves interrupts both afferent and motor paths (i. e.—pelvic and pudendal nerves) and the bladder is isolated from central nervous control. There is a period during which retention of urine with overflow may occur and after this the bladder may partially expel its contents automatically (residual urine left in bladder).

5) Transection of spinal cord above sacral region—

- a) Stage of spinal shock. Retention of urine due to tonic contraction of sphincters — catheterisation has to be resorted to.
 - b) Stage of reflex activity — (after 3 weeks) paraplegia in flexion. Bladder may empty automatically (reflex or automatic bladder). Hypertonicity of sphincters is reduced — residual urine of small volume will remain in bladder.
 - c) Stage of failure of reflex activity — retention of urine or continual dribbling of urine (incontinence).
- 6) Section of hypogastric and pelvic nerves or transection of the spinal cord above the entrance of afferent fibres of the hypogastric nerves or injury to or disease of posterior columns (tabes dorsalis) also involving fibres from sacral roots — sensibility of bladder is lost.
- 7) Bilateral lesions of cortical areas 4 and 6 abolishes voluntary control of bladder, resulting in incontinence of urine.

Bladder reflexes are of diagnostic importance and reveal the site of neurological lesions.

Nocturnal enuresis (Bed wetting): This means voiding of urine during sleep, by young children. In older children and in adults, it is due to an organic lesion (lumbo-sacral vertebral defects — spina bifida) or more commonly due to psychological factors or functional neurological disorders. Incontinence in the aged in the absence of an organic lesion, is attributed to impairment of voluntary control by cortical centres,

THE SKIN AND TEMPERATURE REGULATION

The Skin: The skin covers the entire body except the dorsal aspects of the terminal parts of the digits over which nails are seen. The human skin consists of two parts (Fig. 29) which are adherent to each other. The more superficial of these two is known as the epidermis, which is devoid of blood vessels and is itself made of the following layers: Stratum corneum — in this,

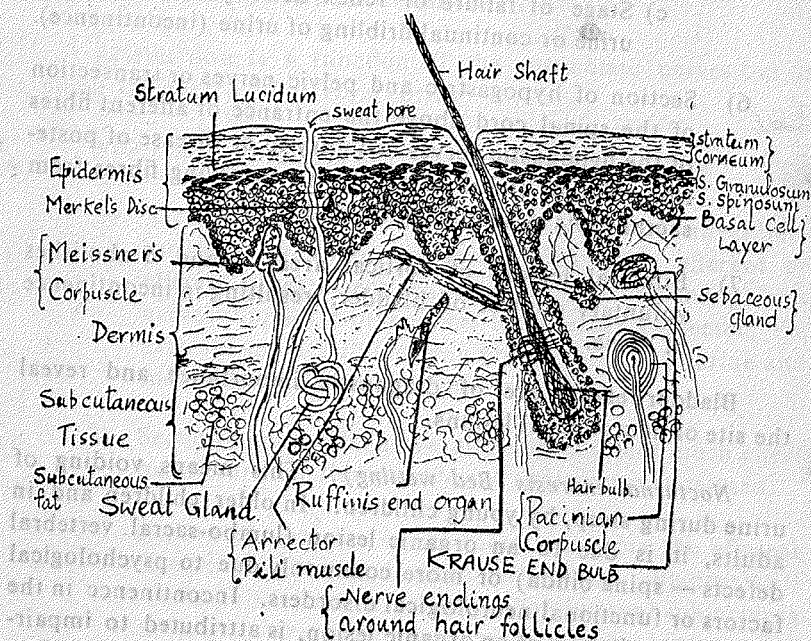


Fig. 29 The Skin

cells are disposed in several layers and these are of the flat squamous type. The cells lying outermost are completely cornified, which means that they contain keratin, a protein. The superficial cells are also devoid of their nuclei and as such should be considered as dead cells. These are shed in large numbers every day as a result of wear and tear and are replaced by cells arising out of the division of those in the deeper layers. The stratum germi-

nativum (Morphian layer) is formed of a single layer of cells which are capable of active mitotic division by means of which it gives rise to the cells of the more superficial layers of the rete mucosum, stratum granulosum, stratum lucidum and stratum corneum from within outwards. This layer (stratum germinativum) is moulded by the dermal papillae which project into the epidermis. The stratum lucidum is a very thin layer just inner to the stratum corneum. The cells in this layer are indistinct in outline and poorly staining. Still inner to this is the stratum granulosum, the cells of which are filled with granules of eleidin which stain deeply with haematoxylin and eosin. All the cells which form several layers and lie in between the stratum granulosum and stratum germinativum, form the rete mucosum, though the term is loosely meant to include all the epidermal layers except the stratum corneum and stratum lucidum. In the deepest layers of the rete mucosum, the cells contain pigmentary granules of melanin. These are found in large amounts in the darker human races. Even the so-called white races are capable of pigment production in their skin, when it is exposed to sunlight. The pigment melanin is synthesized by melanoblasts (melanocytes) which contain an oxidase (tyrosinase). The parent substance for the synthesis is tyrosine, an amino acid. The nails of both the fingers and toes are made of horny material, the cellular basis of which is modified stratum lucidum of the epidermis. The nails act as supporting structures for the digital pads of the terminal phalanges and make possible, in the fingers especially, the extreme sensitivity to touch, at the tips.

The true skin (cutis, dermis) consists of dense connective tissue which merges in its deep regions with subcutaneous tissue. The presence of a large number of fine elastic fibres imparts elasticity to the skin. In old age, these fibres diminish in number and are replaced by collagen fibres, thereby causing wrinkling of the skin. The dermal papillae lodge capillary blood vessels and certain receptors like Meissner's touch corpuscles. Pain nerve endings are also in plenty in the dermis. Arterio-venous anastomoses are seen in the dermis. These are of importance in temperature regulation.

All parts of the skin except the glabrous skin over lips, the palm of the hands and soles of the feet, exhibit hair follicles which

are minute pits extending deeply into the corium and lined by the rete mucosum. At the bottom of the follicle, a small papilla of cells which forms the hair root, gives rise to the hair which consists of long horny cells covered by keratin, the chief protein of the hair.

The skin is kept supple by the fatty secretion, the sebum, which is formed by the glands situated in close association with the hair follicles. Plain muscle fibres forming the arrectores pilorum which have an oblique direction, cause expulsion of sebum (by their contraction) into the hair follicle and thence to the skin surface. Erection of hair also occurs as a result and this gives rise to goose flesh appearance of the skin. These muscle fibres are sensitive to adrenaline and noradrenaline. The sweat glands (eccrine) are present all over the skin (in the corium) and more so in the palms of hands and soles of feet. Each gland is a single tubular and coiled structure, which opens on the external surface of the skin. The ducts have a coiled course through the epidermis (For sweat secretion, see Regulation of Body Temperature).

Apocrine sweat glands are present in certain locations of the body, like the axilla. They give rise to a milky secretion which, when decomposed by bacterial action, is responsible for the offensive body odour.

In the external auditory meatus, ceruminous glands which are similar to the apocrine variety, are found and these secrete a waxy material (ear wax).

Depot fat is stored in the dermis. In women, the fat stores form an insulating layer, giving a smooth contour to a woman's body. They also form an insulating layer against cold.

Functions of skin : While covering the entire body, it serves to protect the underlying parts from trauma and infection by foreign organisms. In view of the abundance of receptors in the dermis, the skin serves as an important sense organ, not only concerned with protection from injurious stimuli, but also in homeostasis. In warm blooded animals, the skin, by virtue of its vasomotor adjustments and sweat secretion, plays a very great role in temperature regulation.

THE REGULATION OF TEMPERATURE

Mammals (including man) and birds are capable of maintaining their body temperature constant and hence are known as homeothermic. Cold blooded animals - the reptiles and the amphibia - have a variable temperature (poikilothermic), which follows the environmental temperature with a slight lag. Even in these animals, high and low temperatures beyond a certain range are inimical to life. This is the reason why they hide under rocks and in shady places during the heat of the day and venture out in the cool hours of the night. In extreme cold weather, they become sluggish and torpid. Homeothermic animals are able to carry on their activities efficiently over a wide range of environmental temperatures.

By body temperature is meant the temperature of the inner core of the body or in other words, the internal organs or viscera (37° - 40°C)

Normal body temperature : A reading should be taken at least 4 or 5 minutes or even more after placing the thermometer in the axilla, mouth or rectum. The oral temperature is 98.4° to 98.6°F or 37°C . The axillary temperature is lower by 1°F than the mouth temperature. Rectal temperature is higher by about 0.5° - 0.7°F than the mouth temperature and consequently nearer to the core temperature.

Cold and hot drinks affect mouth temperature.

A diurnal variation of upto 3°F can occur. The maximum body temperature in the day is at about 4 P. M. and the minimum at about 4 A. M. Working on a night shift will reverse the changes. Temperature regulation is imperfect in infants. Even crying can raise the temperature. In aged people, sub-normal temperatures are seen. Old people are less tolerant of extreme variations in temperature.

During menstrual cycle, a momentary fall in temperature (at ovulation) occurs and this is followed by a rise which slowly declines over several days.

In exercise, a rise of several degrees is seen, especially after running long distances.

The skin has a lower temperature than the inner organs and it is somewhat variable. The temperature gradient between inner organs and the skin facilitates the loss of heat from the body. In hot environments, the gradient may be in reverse direction. The body temperature is maintained constant due to a balance between heat gain and heat loss.

Heat gain occurs, to a major extent, by the production of heat by various metabolic processes which will be elaborated further, subsequently. On a hot day, the body gains heat not only by radiation from the sun if the body is exposed to it but also from hot food and from warm objects in the environment. Since chemical reactions contribute to heat production, the mechanisms of raising the body temperature go by the term 'chemical regulation'.

Heat is lost from the body mainly by the physical mechanisms of radiation, convection, conduction and evaporation. Hence, these comprise 'Physical regulation'.

Vasoconstriction or vasodilatation of the cutaneous vessels may occur to facilitate physical regulation either by preventing uptake of heat from the environment or by increasing the radiational loss (by increasing blood flow to the skin). Sweat secretion is also promoted by nervous mechanisms and cutaneous vasodilatation. In other words, physiological adjustments are necessary adjuncts to physical and chemical processes in thermoregulation.

Chemical Regulation: a) Metabolic activities of liver and heart and other organs produce, usually, a constant amount of heat known as the basal metabolic rate (BMR) which is 40 K cal/hour/sq. M, (1700cal/day) in the male adult, less in women and higher in children (in proportion to their body surface but not in absolute value).

b) Contraction of skeletal muscles contributes a variable amount of heat, depending on the severity of contraction. Severe exercise can increase heat production upto 16 times the basal level. With heavy work, total daily output can be as high as 6000 calories. With the body specific heat being 1 (approx.), it will show a gain in temperature of 2°C. But heat losses are so efficiently controlled that actually very little rise in temperature is seen.

Gain from environment : a) By radiation from the sun, hot furnaces, hot earth and from the sky by reflection. These can be reduced by clothing, or by remaining in shade. Naked skin increases heat gain of the body.

b) On a hot day, hot air can also cause heat to be gained by the body. This is a serious cause of discomfort in tropics.

Heat loss : 1) Physical and 2) Physiological.

1) Physical regulation : The various factors that contribute to the loss of heat and their proportions are mentioned below :

a) Radiation	— 50%	— 1500 cal
b) Convection	— 15%	— 450 cal
c) Conduction	— negligible normally	—
d) Evaporation from skin and lungs and loss through CO ₂	— 30%	900 cal
e) Warming inspired air	— 3%	90 cal
f) Urine and faeces (heat lost in excess over heat of food and water injected	2%	60 cal

100%	3000 cal
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Most of the heat (95%) is lost by (a) and (d).

a) **Radiation** : The body covered by the skin behaves like a black body, in physical terms an efficient radiator and obeys the physical laws of radiation. The rate of heat loss depends on the temperature of the skin and that of the surrounding objects. The body loses heat, if surroundings are cooler and if the objects in the neighbourhood are warmer, actual heat gain may result, as in subjects working near furnaces and boilers. 70–80% of the skin area takes part in radiating heat and hence posture has some importance in radiation. On a cold day, huddling or folding up of limbs with bending forward of the neck is a familiar posture adopted in the absence of adequate clothing or artificial warming aids. Clothing minimises the effective radiating surface and thus reduces radiation. Humid air, when present next to the skin, blocks radiation.

b) **Convection** : Air, in contact with the body, is warmed and moves away from the body giving place to cooler air which is now warmed in turn and these movements of air are repeated. This results in loss of heat. At air temperatures of 34.5°C , convection cannot bring about heat loss. At higher air temperatures, the body gains heat from the movement of air.

c) **Conduction** : Very negligible loss occurs by this means, unless the skin is in actual contact with cooler or cold objects. Air is a very poor conductor of heat. The skin temperature depends on its blood flow and the tone of its blood vessels which is under efficient vasomotor control.

d) **Evaporation** : i) **Insensible perspiration** : This is not due to sweat glands. Water seeps through the skin from the underlying blood vessels and evaporates. This is independent of environmental factors. It amounts to 600–800 ml/24 hrs.

ii) **Sweating** — see below.

iii) **Lungs** : Expired air saturated with water vapour helps to lose 300ml of water or 200 calories per day. Heat is also lost by raising inspired air to body temperature.

2) *Physiological mechanisms for loss of heat :*

Sweat glands : They are of two kinds — Eccrine and Apocrine. The apocrine glands are not of much importance. Eccrine glands put forth a watery fluid (sp. gr of 1002–1003 and pH 4.2–7.5) having very little sodium chloride, urea and lactic acid. In profuse sweating, urea concentration falls, with sodium chloride and potassium increasing. But, if sweating is prolonged, salt concentration falls in order to conserve sodium. The salt concentration depends on adrenocortical activity. These glands are supplied by sympathetic cholinergic fibres which can be paralysed by atropine. Sweat secretion occurs in the following conditions :

i) Thermal sweating — provoked by rise of body temperature and reflexly from stimulation of skin.

ii) Mental sweating — in palms, soles of feet etc. — due to impulses from higher centres. Excess secretion of this type is called hyperhidrosis.

iii) In exercise — both thermal and mental factors operate here.

iv) Due to sympathetic activity—in fainting, vomiting, asphyxia etc.

v) After eating hot spicy foods. This is known as gustatory sweating.

Thermal Sweating : This is useful in promoting heat loss only in dry surroundings. If the atmosphere is humid and hot, sweating goes on, resulting in loss of water and salt but not heat. The maximum rate of sweating is about 1.7 litres/hour. Heat loss can be controlled by alterations in rate of sweat production. At a sweating rate of about 5.5 litres/day, 3000 calories could be lost. One can survive on a dry day with a temperature of even 240° — 260° F, but not on a wet day with a temperature of 130° F. Body temperature will rise steeply in the latter case. Large cutaneous blood flow to facilitate increased sweat secretion is brought about by (i) warmth acting on vessels directly.

- ii) Reflexly, by stimulation of cutaneous warmth receptors.
- iii) Warm blood stimulating the medullary vasomotor centre and hypothalamic heat loss centre.

Polypeptides like bradykinin may also have a role in vasodilatation.

Nervous regulation: There are two mechanisms operating with regard to this.

- 1) Reflex — elicited by stimulation of cutaneous thermal receptors.
- 2) Central — effect of warm or cold blood reaching the medullary vasomotor centre and hypothalamus.

Effect of reflex mechanisms: Sweating, vasomotor changes, fainting and shivering are the main effects of excitation of the reflex mechanisms. Shivering occurs even when only one part of the body is suddenly chilled.

Central Mechanisms: Section of the neuraxis at a level between the superior colliculi and the lower cervical cord makes an animal poikilothermic. In man, a similar effect is seen in the case of injury to the pons and medulla. Section of the upper thoracic cord (above the emergence of sympathetic fibres) abolishes physical regulation, but leaves chemical regulation unaffected, as the muscles of the forelimbs are still innervated. So, heat regulation centres must be above the superior colliculi. Removal of the cerebral cortex, thalamus or corpus striatum does not interfere with heat regulation, if hypothalamus is left intact. Warm blood, when it bathes the anterior hypothalamus, causes vasodilatation. The heat loss centre is said to be situated here. Injury to the anterior hypothalamus, while it leaves the response of the body to cold unaffected, impairs the ability to withstand external heat. Opposite effects are seen in the case of lesions of posterior hypothalamus which initiates bodily reactions to fall in external temperature. Since the descending fibres from anterior hypothalamic heat loss centre pass backwards

either through or in the immediate neighbourhood of the posterior hypothalamic heat gain centre, a lesion in the posterior hypothalamus may even abolish physiological responses to both warmth and cold and render the animal poikilothermic. Hypothalamus receives afferent input from the body and it can control, in its turn, glandular and muscle activity. In animals, centres controlling heat loss (sweating and panting) are placed in the pre-optic and supra-optic regions between anterior commissure and optic chiasma. Heating this area provokes heat loss. Heat production centres are in the caudal part of lateral hypothalamus and identical with the sympathetic hypothalamic centre. Shivering centre is in the posterior hypothalamus. Afferent pathway for shivering is not known. But, spino-thalamic tract may contain fibres concerned with it. The efferent pathway is probably the tectospinal or rubrospinal tract. In man, the reticulospinal may replace the rubrospinal tract. For shivering to occur, the cerebellum must be intact and afferent fibres from the muscles should also be functioning. Cooling of skin periodically, stimulates shivering. Heat loss is also increased by setting up convection currents in the air in contact with the skin. Shivering is reduced by CaCl_2 . Heat regulating centres in man may be situated in similar regions in the hypothalamus as in animals and also in the substantia grisea near the floor of the 3rd ventricle. Lesions in the supra-optic region will be accompanied by hyperthermia (see hypothalamus under Nervous System). The main heat regulating centres are influenced (1) reflexly from skin and (2) by temperature of blood bathing them. Posterior hypothalamus promotes rise in temperature through sympathetic nerves to cutaneous vessels, sweat glands and pilomotor muscles. Removal of this area results in increased susceptibility to cold.

It is pertinent to mention in this context about arterio-venous anastomoses—large vessels shunting blood from the arteries directly to the venous vessels and situated in certain parts of the skin—palmar surfaces of the hands and plantar aspects of the feet, the lips, nose and ears, which are exposed to cold and are liable to be cooled severely on account of their extreme peripheral location in respect of the heart. These vessels have well developed muscular coats which receive innervation from the

sympathetic vasoconstrictor nerves. These release noradrenaline at their terminals. When the body is exposed to cold, blood is diverted away from the cutaneous vessels to flow through these shunts thereby avoiding radiational losses. On the other hand they become constricted when blood has to spread in cutaneous vessels, in order that heat loss by radiation is promoted.

In other situations of the skin where such shunts are absent, changes in the lumen of the arterial vessels can still cause large alterations in the blood flow. When the body temperature tends to rise, these vessels dilate to as much as thrice their normal diameter.

General anaesthetics and chlorpromazine abolish temperature regulation as effectively as injury to pons and medulla. Curare, by causing paralysis of muscles, abolishes shivering.

Chemical and Hormonal Regulation :

A low external temperature (between 28° and 31°C) stimulates heat production. In the naked state, at environmental temperature 28° — 31°C the male body can easily maintain heat balance. No sweating and no shivering will occur. This is called 'comfort zone'. For women, the comfort zone is between 27° and 33°C . Below 28°C , for man, heat production must be increased to maintain the temperature and this is called 'critical temperature'. Below the critical temperature, heat loss by convection and evaporation does not change, but that by radiation increases. At about 23°C and below, shivering occurs and heat production is increased. In nude men, under basal conditions, BMR remains constant between 23° and 35°C . In women, heat production is reduced between 30° and 32°C . Also, because of a layer of sub-cutaneous fat, greater insulation is provided against heat loss, in women. They do not shiver at temperatures at which men shiver. Critical temperature and comfort zone vary with clothing. Heat production is suppressed when the human body is immersed for more than 20 minutes in cold water below 4°C . Heat loss increases above and below the critical temperature. In muscular exercise, raised temperature is not due to inability to dissipate heat, but due to the thermostat

being set at a higher level. The specific dynamic action of food is an important source of heat. So, at cold temperatures, protein-rich diet and at warm temperatures lesser protein intake, is recommended.

Hormonal regulation: Exposure to cold causes the release of adrenaline which has a calorogenic effect. But this is only of a very short duration. The release of adrenaline causes certain visible changes like piloerection (hairs standing on their ends in animals). In human beings this effect is purposeless. Goose flesh is the term applied to the appearance of human skin in which the hair roots are raised from the skin surface and become prominent. In animals, the raising of the fur brings about trapping of air in the coat. Thus, an insulating cover is provided for the body.

Thyroid: Thyroid also puts forth its secretion in larger amounts than normally, on exposure to cold. Since there is a certain lag of time for the thyroid response, it is not functionally significant. To elicit an effective response from the thyroid, the exposure to cold should be a prolonged one. (The adrenal cortex also responds similarly). The effect of cold on thyroid is mediated through the hypothalamus and anterior pituitary. It is well known that myxedematous patients and thyroidectomised subjects cannot tolerate a fall in environmental temperature because of the absence of an adequate thyroid response.

Effect of Exercise on temperature regulation:

Cutaneous blood flow is increased so that skin temperature will rise and a greater temperature gradient is established between skin and environment. Also, sweat secretion is increased and more heat is lost by evaporation of sweat.

Effect of environmental changes:

Effect of a hot bath: After a few minutes in a hot bath (tub), mouth temperature rises, (110°F) the heart rate rises ($75-115/\text{min.}$) and so also the respiratory rate (upto $25/\text{min.}$).

Mouth temperature comes down gradually to normal in about 30 minutes. Heart rate and respiratory rate do so, much faster. The rise in body temperature is due to greater metabolism and also due to the heat absorbed from the bath.

Zone of vasomotor regulation is between 25° and 29°C of external temperature. Cooling occurs below 25°C. Above 29°C, convection helps very little and sweating occurs. Above 35°C, all body heat loss is by evaporation. At a certain temperature varying with relative humidity, even evaporation is of no use. So, with increase in surrounding temperature, different responses occur. To summarise, 1) body cools below 25°C. 2) vasomotor regulation is effective between 25°C and 29°C. 3) evaporative regulation takes place above 29°C. 4) Body gets warm at high temperatures (34°C). About 12% of cardiac output is given to skin (variations by 50 times of normal).

When the room temperature is slowly raised, sweating occurs with a long latency, but its start is sudden and coincides with a rise in the internal temperature of the body. On the other hand, sweating also stops with a lag after room temperature has come down and stays at a lower value. The skin temperature may be low due to evaporation of the sweat.

Cardiac output is increased, with a fall in diastolic pressure, as peripheral resistance is lowered by vasodilatation. Plasma volume increases and the heart rate also shows a rise. Systolic pressure is affected to an extent depending upon the fall in peripheral resistance. The erect posture imposes a strain on the physiological mechanisms. Blood supply to the brain is diminished, consequent on vasodilatation. Salt and water loss causes a fall in cardiac output and a low blood flow to sweat glands. This reduces heat loss through sweating and causes a rise in temperature of the core of the body. Skin temperature may rise by as much as 3°C.

Excessive heat loss from body when exposed to cold, is prevented by opening up of A. V. anastomoses by axon reflexes. Skin becomes warm, red and hyperalgesic. At very high temperatures, vasoconstriction may occur to prevent heat gain.

The body can stand a temperature of 250°C , if atmosphere is dry. Critical air temperature for sweating in nude subjects is 31°C and for lightly clad ones 29°C , the average skin temperature being 34°C . A man can sweat even at freezing temperature or below, while performing heavy exercise. Below 30°C , all evaporation is insensible. Above this, the sweat becomes visible and wets a larger area of the body to increase evaporation. The relative humidity of skin, so to say, increases with relative humidity of air. Maximum evaporative cooling, when naked, at 43°C or 52°C when clad, is 30 calories per sq. meter per hour per cm. Hg difference of aqueous vapour. Clad subjects adapt less well than nude ones. Shifts of fluid occur. Increased blood volume at higher temperature of surroundings and fall when exposed to cold. But later, reverse changes occur.

Exhaustion of sweat glands may occur after prolonged exposure. Sweat volume diminishes, Na and Cl contents rise relatively.

Acclimatisation: This phenomenon is of importance in these days of air travel. Exposure to heat causes increased pulmonary ventilation, rise in blood pH, excretion of alkaline urine, fall in B. P. increased pulse and circulation rate, increase in blood volume, sweating with cutaneous vasodilatation and even rise in BMR. If exposure is prolonged, either intolerance or adaptation occurs. Sweat becomes more dilute and it occurs at a lower temperature. Urine is more concentrated. Sweat contains less sodium chloride. Skin temperature may be high, but at rest, body core temperature returns to normal.

Mechanism of acclimatisation is not understood. Loss of weight may cause a smaller mass of metabolising tissue to be endowed with a greater cooling surface. Adjustments in nervous system, endocrines, CVS, water distribution are other factors.

Acclimatisation to work may occur in a few days in hot conditions. Acclimatisation lasts for 2-3 weeks.

Effect of Clothing: Clothes afford protection from high or low environmental temperature because of low conductivity. Air between the layers of clothing acts as an insulator, having

much lower conductivity than cloth. So two layers of thin clothing are better than one thick layer. During exercise, clothing must allow evaporation and so porous clothing is better. Impervious materials like rubber are of no use in this respect. Clothes increase effective radiating surface, but reduce its temperature. Distribution of temperature in skin of a clothed body is different from that in the nude state. Extremities are cooler and trunk warmer, when a person is clothed.

Cooling occurs in the covered body when external temperature is 8°C below skin temperature. But in nude subjects, it occurs when temperature is 4° less. Heat loss for clothed body in indoor conditions is about 45% of total heat loss. But for nude subjects it is 52% due to radiation and convection. Clothing reduces radiation and conduction below temperatures of 0°C . The clothed body has greater conductivity than the nude one. Wet clothing loses its insulating property, as water replaces air in the meshes of the clothing.

Clothing in cold climates : The purpose is to have a layer of air insulating the body. Furs are very useful as air is trapped in the hairs. The cold temperature outside, overcomes the body's attempts to increase the heat production. Cold exhaustion may set in. The reflexes become sluggish and affected people may fall asleep when body temperature (rectal temperature) falls below 25°C (77°F). Death may occur if the body temperature goes below 20°C . Adaptation to cold is of much less degree than to heat, because the artificial aids like clothing actually avoid effects of cold. Even Eskimos are not actually adapted to very low temperatures. They swathe themselves in heavy clothing of skins and fur and this prevents any actual adaptational physiological changes. With modern amenities, low temperatures are better tolerated than high temperatures.

Disturbances of Heat Regulation :

Any alteration in loss or production of heat will cause a disturbance of heat regulation. Temporary derangement may occur due to hot baths which prevent loss through conduction, radiation and evaporation and adds on heat to the body. Also,

in violent exercise, a similar effect is seen. A fall in temperature is much more difficult to produce than a rise, because of efficient (chemical) mechanisms being available for the former but not for the latter. Heat regulation is depressed by anaesthesia, sleep, hypnosis and general fatigue.

The body is able to maintain its temperature provided there is no wide disparity between the temperature of the environment and that of the body. In the case of the former, the environmental temperature can fluctuate over a range from 55°C below that in a temperate zone and 30°C above without causing strain on the heat regulatory mechanism of the body. If environmental temperature is above the upper limit or below the lower limit, the physiological mechanism will be disrupted. The variation in the body temperature which is compatible with life cannot be more than 6°C above the normal or 12°C below the normal.

The body temperature will tend to rise under the following conditions: Strenuous exercise, heavy and impervious (to moisture) clothing, a hot moist environment, a prolonged hot bath, intense radiant heat from the sun or from an artificial source, injections of certain fever producing agents and bacteria organisms. If the high temperature that results on account of any of the above mentioned factors is maintained for an appreciable length of time, any one of following conditions will supervene:

Heat cramps: This condition is seen frequently in miners (miner's cramps) who have to do arduous work in hot, humid surroundings where high atmospheric pressure also exists.

Heat cramps are due to loss of Na^+ and Cl^- in sweat. 0.2% NaCl solution is given to patients to restore lost salt.

Hyperpnoea causes a fall in CO_2 content of blood with resulting alkalaemia and hence urinary NH_3 falls and urine becomes alkaline.

Heat stroke: Heat stroke comes on without warning. Sweat secretion is depressed and unconsciousness results. Rectal temperature is about 110°F. Heat regulation is completely upset.

origin to Bayliss and Starling who, in 1905, used it in respect of Secretin, the first of the gastro-intestinal hormones to be discovered and the first to be called a hormone.

Methods of study of the functions of the Endocrine glands : The methodology in this branch of physiology is well established. Nearly all the following procedures have been made use of in the study of each one of the ductless glands. The final development in this field is the laboratory synthesis in the refined state of some hormones, though many more are yet to be synthesised by the biochemist.

1. Ablation of the gland : This is the earliest of the various methods. Nearly all the glands have been removed selectively to study the effects of their deprivation. The expectation was that the function of the gland could be inferred from the effects of its removal.

2. Grafting of the gland to abolish the symptoms arising out of its removal:— Berthold did this in his pioneering experiments. When the tissue or gland to be grafted comes from the same animal, it is known as autograft. Homografts and heterografts refer to grafts taken from an animal of the same species or of a different species, respectively. Autografts and homografts are much more successful than heterografts. If the consequences of removal are offset by the graft, then it implicates the gland more or less conclusively as regards a particular physiological role.

3. Administration of glandular extracts instead of grafting : Brown Sequard was the first worker to try this. Presuming that the symptoms of ageing were due to deficiency of testicular principles, he prepared extracts of the gland to be used on himself. Murray, the English physician, prepared glycerine emulsions of sheep thyroid tissue for being administered to human sufferers of thyroid deficiency and he should be considered as the first to practise Substitution Therapy.

In the case of glandular extracts, there is species specificity in action. An extract of a gland of one species is most effective in members of the same species and least in other species.

Moreover, extracts from animals of a higher phylogenetic order are effective in those of lower orders only, but not in animals of a level higher than those from which the extracts have been prepared. Further, the intensity of action of an extract wanes off, on repeated administration. This phenomenon is called tachyphylaxis and in some cases, it is due to the development of anti-hormones in the recipient animal.

4. Later developments in Biochemistry have made it possible to work out the chemical structure of the hormones and it has become possible to synthesise some of them. The steroid hormones have been successfully synthesized and even more remarkable than this is the fact that several artificial steroid hormones have been prepared with very specific actions as required in therapeutics, unlike the natural hormones which have more than one action. The chemical nature of the protein hormones is being unravelled more and more and in the near future, it may be possible to synthesize them in the laboratory. At present, most of them are obtained in bulk from the slaughter houses.

Certain general observations have been made regarding the chemical nature of the hormones. Glands which have been embryologically derived from the alimentary canal as off shoots or diverticula, elaborate substances of high molecular weight that are proteins or protein fragments (polypeptids). The thyroid is an exception—its hormone is a substituted amino acid. The adenohypophysis and the islet tissue conform to this conclusion. These hormones cannot be administered by mouth when an effect is desired, as they are certain to be destroyed by digestive enzymes. The parathyroid also gives rise to protein hormones. The next major category is that of the steroids. Endocrines arising out of the coelomic epithelium in the embryo, such as the adrenal cortex and the sex glands, synthesize hormones of the steroid type. Oral route of administration does not reduce their effects very much.

5. Clinical conditions in human patients, arising out of dysfunction of the endocrines, have been studied very carefully and they have been compared with similar states established in

animals experimentally. Almost all such syndromes have been related to the malfunction of one or the other of the ductless glands. Symptoms of excessive action or deficiency of each one of the glands, are now well recognised and various laboratory tests have been evolved to assess the functional status of these organs.

HYPOPHYSIS CEREBRI

Any account on endocrinology should properly begin with the Physiology of the hypophysis or pituitary gland. Though insignificant in size, it has a profound influence over most of the other endocrine glands, the notable exception being the parathyroid. Hence, the pituitary has even been called the master gland or leader of the endocrine orchestra.

This gland, embryologically, develops out of two entirely unrelated tissues. The anterior lobe of the gland, along with the para tuberalis and including the intermediate lobe, arises from the roof of the primitive buccal cavity as a diverticulum known as the Rathke's pouch. The posterior lobe is derived from the floor of the III ventricle. The two lobes develop in close association with each other. The cavity of the Rathke's pouch, along with its stalk from the mouth, disappears during development. The posterior wall of the Rathke's pouch becomes adherent to the posterior lobe and in the adult gland, it is represented by a narrow zone of tissue, the cavity of the Rathke's pouch persisting, if at all, as a row of vesicles. Some confusion has arisen out of the different terms of nomenclature used for the various parts of the hypophysis.

<i>Origin</i>	<i>Primary division</i>	<i>Sub-division</i>
From primitive buccal cavity	Adenohypophysis	1) Pars distalis (anterior lobe) 2) Pars tuberalis 3) Pars intermedia
From floor of third ventricle	Neurohypophysis	1) Infundibular process-neural lobe } posterior lobe Neural stalk { 2) Infundibular stem 3) Median eminence

The adenohipophysis (pars distalis) mainly consists of cords or clumps of cells histologically separated into three types. About half of all these cells are known as chromophobes, not easily stained, as the name indicates. The rest (chromophils) of the glandular cells have been divided into acidophils (35% of the total) and basophils (15% of the total), the names arising out of their staining properties. It is probable that the chromophobes are only the young and immature forms of the chromophil cells (acidophils and basophils). Enough is known about the chromophil cells to assign secretory activity as regards the various hormones. Based on observations made after the removal of certain endocrine glands, cells of the hypophysis have been classified as castration cells (signet cells), thyroid cells and certain cells seen during pregnancy. The basophils have been divided into thyrotrophs, diffusely distributed all over the gland, central gonadotrophs (in the central portion of the gland) and peripheral gonadotrophs. The acidophils are of two kinds - orangeophils secreting the growth hormone and carminophils responsible for prolactin.

Effects of total hypophysectomy: On account of the involvement of the adenohipophysis in the regulation of the activity of other endocrine glands, the effects are manifested as deficiency of the target glands.

- 1) Atrophy of the thyroid with consequent lowering of BMR and other related features.
- 2) Atrophy of the adrenal cortex with its attendant symptoms.
- 3) Arrest of sexual development and absence of pubertal changes in immature animals. In post - pubertal men and women and in adult animals, suppression of sex functions.
- 4) Susceptibility to insulin with fall in blood sugar level.
- 5) Mild diabetes insipidus.
- 6) Arrested skeletal growth in young animals.

From the above-mentioned changes seen after hypophysectomy, it became evident that a number of hormones were elaborated by the adenohipophysis which is now believed to synthesize six well recognized hormones.

- These are
- 1) Growth hormone or somatotrophin
 - 2) Thyrotrophin or thyroid stimulating hormone (T. S. H.)
 - 3) Adrenocorticotrophic hormone (ACTH)
 - 4) Gonadotrophic hormones - a) Follicle—stimulating hormone (F. S. H) b) Luteinising (L. H.) or Interstitial cell stimulating hormone. (I. C. S. H)
 - 5) Lactogenic hormone (prolactin, Luteotrophic hormone)
- All the fore - mentioned hormones are proteins in nature and these are ineffective if administered orally.

Growth Hormone: The role of this hormone in promoting growth was brought to light by the occurrence of dwarfism in animals after hypophysectomy and in human beings (congenital absence or maldevelopment of the gland). The human growth hormone is a protein fragment of molecular weight between 20,000 and 30,000. It promotes skeletal growth and development of viscera—compensatory hypertrophy of certain viscera after partial removal is believed to be due to the action of this principle. Growth seems to be due to a concerted action of somatotrophin and the hormone of the thyroid gland which is concerned with tissue differentiation and maturation. The growth hormone produces a profound anabolic effect with retention of nitrogen, the new protein formed being retained, promoting growth. This hormone is species - specific, the extract from the gland of an animal of one species being effective only in the same species. The acidophil cell (alpha cell) is responsible for its secretion, as deduced from the fact that Eosinophil adenomas are seen in some cases of gigantism. Disorders arising out of excess secretion or deficiency will be described subsequently.

Injection of a large dose of the growth hormone produces a transient condition known as hypophysial diabetes mellitus (to be described in greater detail later on). Repeated injections bring about a permanent condition called metahypophysial diabetes ('Young' animal). These facts implicate the growth hormone in the causation of disorders of carbohydrate metabolism. The older authors were led to suspect the presence in the gland, of a few hormones known as diabetogenic, ketogenic and glucostatic factors. It is now well established that the diabetogenic effect is

only a side action of the growth hormone itself. The presence of insulin in adequate amounts is thought to be necessary for the normal physiological role of the growth hormone. The protein-sparing action of insulin is possibly involved in it. The physiological role of the growth hormone in adults has not been revealed. It is possible that an excess of growth hormone may be a causative factor, at least in some cases of diabetes mellitus. The unbalanced diabetogenic effect in such cases may lead to an exhaustion atrophy of the pancreatic islets.

Thyrotrophin: The thyroid gland is under the control of pituitary through its hormone, thyrotrophin, considered to be elaborated by the basophil cells. The thyroid itself is figuratively called the target organ of the pituitary hormone. Similarly, the adrenal cortex and sex glands are target organs for other pituitary 'trophic' hormones. The relationship between such a pituitary hormone and its target organ is well established by the results of hypophysectomy which brings about atrophy of the target gland. The parathyroid gland does not atrophy after the removal of the pituitary and so it is believed that there is no pituitary control over its function. A trophic hormone promotes not only the growth and development of the target gland to attain its appropriate status in the adult, but also is responsible for the maintenance of the normal secretory activity of the target gland. The thyrotrophic hormone seems to be a glyco-protein of molecular weight about 28,000. Its role as regards thyroid activity is discussed in detail under "Thyroid".

Adrenocorticotrophic hormone (ACTH): It is not possible to identify the cells of origin of this in the pituitary gland for this hormone, though the basophils cannot be conclusively excluded in this regard. The occurrence of a basophil adenoma, in association with the hyperfunction of the adrenal cortex, has been observed by many workers. All the same, there is some evidence that the tumor and the symptoms of hyperfunction of the gland may not have a cause and effect relationship between them. This hypophysial principle is a protein of molecular weight around 20,000. Its function as regards the regulation of the cortical function, is relegated to the discussion on the Adrenal cortical gland, later.

Gonadotrophic hormones: An account of the physiology of these hormones is reserved to a later stage. The two well-established gonadotrophins, namely - Follicle Stimulating Hormone (F. S. H) and Luteinizing hormone (L. H.) are glycoproteins in nature. The basophils or β cells may be responsible for the release of gonadotrophins and there may be two types of β cells, each secreting one of the gonadotrophins.

Prolactin: An account of the physiology of prolactin will be found under the heading, 'Lactation'. The acidophil cell seems to be the secretory cell. This hormone also is a protein. The lactogenic hormone is to be considered as the third gonadotrophic hormone (Luteotrophin) concerned with the development and secretory activity of corpus luteum. Control of sexual functions of anterior pituitary is effected by:—

- 1) Ovary, testis and adrenal cortex, acting by way of the feedback mechanism.
- 2) Reflexes initiated by copulation, exposure to bright light etc.
- 3) Nutritive factors like vitamin E and states of undernourishment.

The regulation of the secretion of the Anterior Pituitary gland:

There appears to be a dual control over the secretory activity of the adenohypophysis. a) Neurohumoral control operating through the hypothalamus and its "releasing" factors. b) Negative feedback or "servo - control".

a) *Neurohumoral mechanism:* The work of Harris and his collaborators have elucidated this mechanism. There is a portal system of blood vessels providing drainage from hypothalamic sinusoids into the capillary vascular spaces in the substance of the pars distalis. It is believed that certain stimuli applied to the body surface or specialised receptors like the retina, provoke the liberation of so-called releasing factors by neuro secretory cells in the hypothalamus. These humors are absorbed into the vascular plexuses in the

hypothalamus and conveyed to the pituitary gland by the portal vessels. Having obtained access to the pituitary secreting cells, they bring about the liberation of hypophysial hormones. It has been further worked out that for each of the pituitary factors, there is a corresponding releasing factor in the hypothalamus. It has even been further established that each region in the hypothalamus is responsible for a particular releasing factor and cells releasing these factors are called thyrotrophs, corticotrophs and so on.

b) Negative feedback mechanism : The secretory activity of pituitary cells seems to be profoundly influenced by the blood levels of the hormones of the target glands. Thus, the release of each trophic hormone is affected in a see-saw manner by its 'target' hormone. Initially, as the pituitary puts forth more and more of its trophic hormone, there is a rise in the blood titre of the hormone of the target gland. When the latter rises above a certain level in the blood, further release of the trophic hormone is prevented. Such a mechanism has been termed as a negative feedback or servo-control, as a parallel from engineering practice. The inhibitory effect of the target hormone on the pituitary activity is believed to be twofold. This action is exerted partly directly on the hypophysial cells and partly by an effect on the hypothalamic cells modifying the output of the releasing factors themselves and thereby affecting the level of activity of the pituitary secretory elements.

The mechanisms controlling the secretion of the pituitary gland have also been dealt with in the accounts on the individual target glands.

NEUROHYPOPHYSIS

The structural elements forming the posterior lobe do not include any obvious secretory cells, except for certain peculiar ones called Pituicytes. The rest comprise of nerve fibres, blood vessels and neuroglial cells. Pituicytes are fusiform cells with many processes and containing a brown pigment in the cytoplasm. In addition, certain structures called Hyaline bodies

are present. The fine nonmyelinated nerve fibres can be stained by special silver impregnation (Gomori stain). The supra-optic and para-ventricular nuclei of the hypothalamus send down nerve fibres into the substance of this gland. Since no secretory cells are present, it is becoming more and more certain that neurosecretory cells, in the above mentioned nuclei of the hypothalamus, elaborate the so-called neurohypophysial hormones which find their way along the nerve fibres to be stored in the posterior pituitary lobe. The supra-optic nucleus is held to be responsible for the antidiuretic principle, and the para-ventricular nucleus for oxytocin.

The crude extract of this gland going by the name pituitrin was first tried on animals, to learn about the role of this gland. Certain effects were noted which could not be confirmed when purer extracts were obtained later. Further chemical purification led to the isolation of two active principles with separate and distinct actions. They have been named the antidiuretic hormone and oxytocin. The former, when administered in large pharmacological or unphysiological doses, has a pressor effect, giving the reason for its being named as Vasopressin. The actions of these hormones are considered below in detail.

Antidiuretic hormone (ADH):— This has been purified sufficiently to yield a polypeptide of eight amino acid residues; six of which are common to both the posterior pituitary principles. Isoleucine and leucine are found in oxytocin, instead of phenylalanine and arginine as in ADH. The main action of this hormone is manifested as the concentration of urine in the distal convoluted tubule and collecting tubule. After the reduction in volume of the glomerular filtrate in the proximal portions of the renal tubules (obligatory reabsorption amounting to 85% of the total), the tubular fluid undergoes further reduction in volume in the distal and collecting tubules, depending on the availability of the antidiuretic hormone. The maximum extent to which reduction can be achieved, as a result of hormonal action, is 15% (facultative reabsorption), yielding about 1–1½ litres of urine finally. Due to the peculiarity in the shape and disposition of the renal tubules and the blood vessels in the juxtamedullary regions as well as in the outer medullary regions, a condition of

hypertonicity obtains in the extracellular fluid surrounding the hairpin-like bent portion of the Henle's loop and the neighbouring blood vessels. There is a marked tendency consequently, for water to be drawn from the distal and collecting tubules, provided the walls of these tubular segments are made permeable to water. In the absence of sufficient amounts of antidiuretic hormone, urine cannot be concentrated beyond what has been achieved in the proximal portions. The concentration of urine in the distal portions is made possible by the action of the antidiuretic hormone which renders the walls of the tubules permeable to water which escapes into the interstitial fluid because of its hypertonicity, the sustained maintenance of which has been attributed to the so-called hairpin counter current system of flow in the Henle's loop and in the neighbouring blood vessels. The underlying hypothesis was put forward by Wirz. The increase in permeability to water of the renal tubule may be brought about by increasing the concentration of hyaluronidase locally. In the total absence of this hormone, urinary output will be maximal and will exceed 20 litres, giving rise to a severe form of Diabetes Insipidus.

As indicated already, the unphysiological action of this hormone in large doses is one of generalised vasoconstriction without sparing any blood vessels. A characteristic feature of the record of the blood pressure after a dose of vasopressin, in an animal, is that of a double rise. The initial rise is attributed to a generalized vasoconstriction, causing a rise both in systolic and diastolic with a concomitant rise in mean pressure. Rise in mean arterial pressure results in heart action being inhibited, this in turn causing a fall in blood pressure with distension of cardiac chambers. The secondary rise is held to be due to a rise in the stroke volume owing to the stretching of the heart muscle fibres.

Oxytocin :— This is so called on account of its excitatory effect on the full term pregnant uterus. The evidence regarding its exact physiological role is conflicting. Nevertheless it looks as if, in the human species at any rate, this hormone is necessary for the normal course of parturition. Hypophysectomy did not interfere with normal parturition in the cat, though in the rat

it caused prolongation of the gestation period. In cases reported from Spain during the civil war, pregnant women who exhibited symptoms of neurohypophysial deficiency such as Diabetes Insipidus, had greatly prolonged labour in successive pregnancies. This shows that oxytocin is necessary for the expulsion of the foetus. This hormone has been demonstrated in the blood of both pregnant cows and women in labour, though a quantitative relationship could not be established between the blood concentration and the vigour of uterine movements. The wide use of crude pituitary extracts by obstetricians, in promoting labour contractions, is adequate testimony to its importance in parturition.

Another action possessed by oxytocin is in augmenting the flow of milk from the lactating breast. The act of suckling by the newborn infant, sets up impulses in the nipple and these are conveyed to the hypothalamus along nerve pathways. Oxytocin which is released from the hypothalamus is carried in the blood stream to the breast where it excites the myoepithelial cells in the walls of the alveoli and the ducts, to eject the contained milk. It is a well known fact that when a cow is milked, initially very little milk flows, but when the teats are stimulated sufficiently, profuse flow follows after a short interval. This phenomenon was attributed to the release of an unknown "let-down" factor which now has been identified as oxytocin.

It is also possible that after the act of copulation, oxytocin may be released to act on the uterus, producing contractions which actively assist the ascent of spermatozoa upwards along the uterine wall.

Control of neurohypophysial activity: The posterior lobe has intimate nerve fibre connections with the hypothalamus and hence it is subject to nervous influences operating through the hypothalamus. An instance of such a mechanism has already been referred to with regard to the ejection of milk and this is described as a neurohumoral reflex. The afferent limb is made of neurones and the efferent, a chemical or hormonal factor liberated into the blood to be carried to the effector organ to act on it.

The secretion of the antidiuretic hormone seems to be, as postulated by Verney, under the regulating influence of certain specialized receptors in the hypothalamic nuclei, termed osmoreceptors. A rise in the crystalloid osmotic pressure in the plasma excites the osmoreceptors, perhaps by abstracting water from them. This in turn brings about the liberation of the antidiuretic hormone which, acting on the distal part of the tubules, promotes reabsorption of water and thereby brings down the crystalloid osmotic pressure, the rise of which was the original stimulus. On the contrary, a fall in the crystalloid osmotic pressure will result in diminishing the ADH output and help to lose water, thus allowing the crystalloid osmotic pressure to rise. This view has been substantiated by experimental studies wherein the osmotic pressure was altered and the changes in the urinary output were noted.

Disorders of Pituitary Function: These can be of two categories, one resulting from a deficiency or hypersecretion of anterior lobe hormones and the other pertaining to posterior lobe hormonal output. Overactivity of the adenohypophysis gives rise to gigantism in children or acromegaly in adults when the offending hormone is somatotrophin. When ACTH is implicated in hyperactivity, Cushing's disease results.

Gigantism: Excessive secretion of the growth hormone, occurring in childhood (eosinophil adenoma seen in some cases), produces enormous skeletal growth and such individuals are of great height—more than 6½ feet. The limbs are very long in proportion to the trunk, though there may be no splanchnomegaly.

Acromegaly: Excessive secretion of the growth hormone in the adult, commencing after full skeletal growth is attained, gives rise to this condition. Certain bony abnormalities are the notable features of this condition. Overgrowth of the bones of the face, hands and feet are characteristic features. The molar and nasal bones are enlarged. The mandible becomes very prominent. The supra-orbital ridges are also thickened. The skin of the scalp is thrown into folds. The face assumes a coarse expression. The digits of the hands and feet are greatly increased in size (spade-like hands). The terminal phalanges are widened. The

vertebral column becomes bent forwards (kyphosis) the hands reaching upto the knees. The individual appears to take on a simian or ape-like attitude (reversal to gorilla type). Enlargement of viscera – splanchnomegaly is an accompanying feature. Hyper-activity of the target organs may also occur. Suppression of sexual functions and reduced tolerance to glucose (Diabetes mellitus) may be seen.

Cushing's Disease: The symptoms of this condition are really the result of overactivity of the adrenal cortex which is whipped up by a large output of ACTH from the pituitary. When the hypophysis is primarily responsible, the condition is known as Cushing's disease, while the term Cushing's syndrome is applied, if the fault lies primarily in the adrenal cortex.

Conditions arising out of deficiency of anterior pituitary hormones with particular reference to growth hormone: The commonest disorder is dwarfism, of which two types may be seen. More often, the pituitary dwarf resembles a human adult in miniature, the trunk and limbs bearing a normal proportion, except for the head which is slightly larger. The intelligence of these individuals, though not of a high order, yet is of sufficient degree to carry on fairly useful lives. Sexual functions may or may not be suppressed and these individuals are known to have offsprings of their own. The height may not exceed 3 – 4 feet and the general appearance is rather pleasing. 'Lorain type' is the name assigned to this condition. Children of this category are said to be angelic in appearance. Occasionally, however pituitary dwarfs may present a wizened or emaciated appearance, the apparent age seeming to be much more than the chronological age, as a result of senile changes occurring prematurely. Progeria is the term used for this condition. Comparison is often made between a cretin and a pituitary dwarf. The former has all the characteristic stigmata of hypothyroidism, the most marked of which are very poor mental development resulting in idiocy, low B. M. R and an abnormal myxedematous skin. In other words, the cretin leads a vegetable existence. The pituitary dwarf, both physically and mentally is on a much higher plane, leading a fairly useful life, often having children of his own. It is however observed, that the life expectancy in hypopituitarism is much shorter than in normal individuals.

Simmond's Disease : This condition results from an atrophy of the anterior lobe, occurring often in women, following childbirth. The stress of parturition may give rise to haemorrhage into the glandular substance and consequent glandular destruction. The activity of target organs also will be very much depressed. Loss of body hair and sparsity of hair over the scalp, wrinkling of the skin, marked loss of weight with shrunken face, are some of the important features. Suppression of sexual functions and hypo-activity of the adrenal cortex and the thyroid make the individual a miserable specimen. Early death may ensue in these individuals.

There is no clinical condition as yet recognized, resulting from overactivity of the neurohypophysis. The one well-known entity arising as a consequence of deficiency of neural lobe hormones is diabetes insipidus. The causative lesion may be either in the pituitary gland or the hypothalamus and as such, this disease is to be considered as a hypothalamico-hypophysial disorder. In the hypothalamus, the supra-optic nucleus along with the fibres of the tract arising out of it and given off to the neural lobe, may be involved in the disease process. Voiding of large amounts of urine of low specific gravity (1002 - 1005), is the hall-mark of this condition. In the total absence of the antidiuretic hormone, the urine volume may be as much as 30 litres and consequently treatment of this condition has to be directed at making up of the water loss. Intense thirst is a prominent symptom. Increased hunger may also be associated with it. Food intake has to be increased in order to help in the maintenance of body temperature which is prone to be disturbed by intake of large quantities of water necessary to sustain life. The removal of the anterior pituitary lobe and the thyroid seems to cause an amelioration of this condition. Administering the glandular extract or the gland tissue, dried and powdered in the form of "snuff" are well known methods of treatment.

Dystrophia adiposo-genitalis : This is believed to be a consequence of a lesion involving the anterior lobe as well as the posterior lobe and even the hypothalamus. It is of two types, the infantile and the adolescent or adult type. The former which

is also known as Frolich's syndrome, occurs in children before puberty. Stunted growth, marked obesity, polyuria and high sugar tolerance, are seen in this. A voracious appetite with a tendency to fall asleep quite frequently even during day time, may be seen. In literature, 'the fat boy' of Dicken's novel 'Pickwick Papers', provides an accurate picture of this condition. In adults, extreme adiposity of the trunk with thin limbs ending in small and pretty feet and hands, are the features. Sparsity of body hair is an additional feature. Diabetes insipidus and narcolepsy are also seen.

THE THYROID

The name of this gland arises from its resemblance to a shield (Thyreos—Greek for shield). This gland seems to have had a digestive function early in phylogeny. It is developed from a diverticulum arising from the floor of mouth in embryonic life. The terminal part of the offshoot divides into two portions which form the lateral lobes which are connected to each other by means of an isthmus. The intervening link between the gland and the mouth usually disappears completely but occasionally remnants are present in the form of thyroglossal cysts or even accessory thyroids.

An average human thyroid gland weighs about 25 G. (larger in women who have borne children) being made up of a large number of alveoli or acini; these are lined by epithelial cells varying in shape, from being flattened to columnar variety, depending on the activity of the cell. The usual shape is cuboidal, indicative of moderate activity. The luminal surface of the cell shows microvilli characteristic of an absorptive function. The acini contain pink (on staining) colloid material which is thyroglobulin, the storage form of the hormone of the gland. The thyroid is an exception among ductless glands in that, a pre-formed hormone is stored ready for release when required. This gland is endowed with a very rich blood supply. There does not seem to be any nervous control over the activity of the gland. The autonomic nerve fibres found in the substance of the gland may have only a vasomotor function.

Biosynthesis of the thyroid hormone: The hormones of this gland are derived from the amino acid tyrosine and iodine, one of the so called trace elements. The thyroid has the remarkable property of abstracting iodide radicals from the blood and concentrating the iodide group by about 25 times, normally. This mechanism is figuratively termed as the Iodide Trap. The absorbed iodide is oxidised to elemental iodine by an enzyme, the peroxidase. These two steps of concentration and oxidation are interfered with by thiocyanates and perchlorates. Next in the sequence of reactions of hormonal synthesis is the iodination of the tyrosine molecule, to successively yield mono-iodotyrosine and di-iodotyrosine. This is blocked by drugs of the thio-uracil group. Two molecules of di-iodotyrosine are coupled, resulting in tetraiodothyronine or thyroxine, the major hormone of the gland. To a much less extent is the formation of tri-iodothyronine arising out of the combining of a molecule of mono-iodo tyrosine and one of a di-iodotyrosine. The sequence of the steps is represented below.

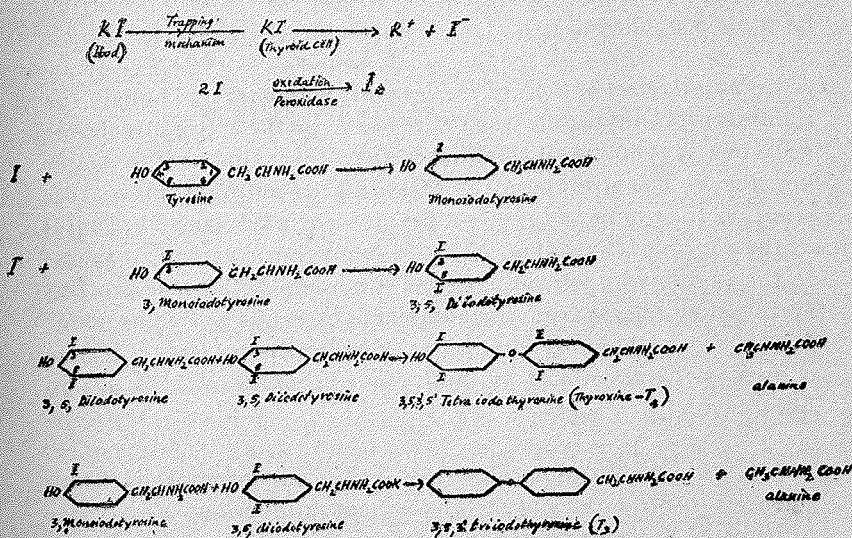


Fig.50 Biosynthesis of Thyroid Hormones

It is curious that iodine, in the form of Lugol's iodine, suppresses the synthesis of the hormone, though how this is brought about has not been understood. This fact has been made use of in the pre-operative treatment of thyrotoxicosis, to render the gland less friable, less vascular and more firm to make its surgical removal easy. The thio-uracil group of drugs, while interfering with the biosynthesis, makes the gland friable, more vascular and consequently hazardous for removal.

In the stored form of thyroglobulin, the hormone forms part of a giant protein molecule. A proteolytic enzyme splits off the active hormonal fragment enabling its release into the blood stream, in which it is carried attached to the albumin fraction and a globulin of plasma proteins. The drugs perchlorate, thiocyanate and thio-uracil have been used therapeutically in cases of hyperthyroidism. The propyl and methyl derivatives of thiouracil are found to be even more efficacious. Thyrotrophin of the pituitary has a key role in the synthesis of the thyroid hormones. It influences the process at all stages, though the earliest effect of its administration is the accelerated release of the hormone from its protein bondage.

Physiological actions of the thyroid hormones: Though for a time tri-iodothyronine was believed to be the active circulating hormone, it is now well established that thyroxine is the major hormone. The misconception regarding tri-iodothyronine, arose from the long latency (of a few days) associated with the onset of the action of thyroxine. This has now been explained as due to the avidity with which thyroxine combines with tissue proteins and its slow release from the combined form. The free hormone becomes available only after being slowly dissociated. If one compares the net effects of both the hormones, there is no difference.

The main physiological action of thyroid hormones is Calorigenesis or promotion of metabolic heat production. This seems to be brought about by enhancing the action of oxidative tissue enzymes, though the exact enzyme system affected has not been identified. Mitochondria in tissue slices and tissue homogenates exposed to thyroxine, show swelling and increase in number.

The pronounced effect on the basal metabolic rate is the hall mark of thyroid activity. Basal Metabolic Rate (B. M. R.) denotes the heat production of the body under basal conditions, namely at physical and mental rest. As a practical approximation, the rate of heat production is determined in the laboratory when the subject is in the post-absorptive phase of digestion—that is 12 to 15 hours after the last meal. The subject has to come to the laboratory in the morning without having taken a meal within the previous twelve hours. He breathes from and into a spirometer in which a known volume of oxygen has been enclosed and the expired carbondioxide is absorbed into caustic soda or potash, the whole set up forming a closed circuit. The oxygen used up over a known period of breathing is measured and the rate of its utilisation determined. Knowing the heat production for every litre of oxygen utilised, BMR can be derived. An average value for a normal male adult is 40 kilo calories/hour per square metre body surface. The value for women is less and in children it is higher, because of growth. Physical or mental activity increases it appreciably and that is the reason to exclude them during the determination of the BMR. The BMR is lower during sleep. All values are expressed as percentages above or below the normal.

The rise in heat production resulting from thyroid stimulation is reflected as a rise in the rate of oxygen utilisation of all tissues except the brain.

Thyroxine has a pronounced effect on the maturation and differentiation of cells during growth. This is nowhere better seen than in the case of the brain tissue. The development of the nervous system and that of the intellect is dependent on adequate levels of blood thyroxine. A cretin is markedly retarded intellectually. Cretinism should be diagnosed at a very early age in order that treatment is started at the earliest possible moment. If treatment is delayed, serious mental retardation will result. In amphibia, metamorphosis is accelerated by thyroxine, the tadpole becoming a dwarf frog in a shorter time than usually. A thyroidectomise tadpole remains as such and will assume a gigantic size. The axolotl which is an aquatic creature with gills for breathing, develops lungs and becomes a land animal, under the influence of thyroid fed to it.

Thyroxine in physiological amounts, promotes protein synthesis and thereby growth, but excess of hormone brings about breakdown of protein resulting in nitrogen loss and bodily wasting.

Thyroid hormones are hyperglycaemic agents, though they promote tissue oxidation and glycogenolysis in all tissues. Neoglycogenesis is favoured by thyroxine.

Diuresis results from thyroid administration. Potassium elimination due to cellular breakdown, is a side effect. In hyperthyroidism, Calcium excretion is increased leading on to rarefaction of bones. The conversion of β -carotene to vitamin A is promoted by thyroxine. Skin discolouration to a yellow hue in hypothyroidism is due to accumulation of β -carotene.

Anaemia is seen as a constant feature in hypothyroidism. Thyroxine is responsible for normal erythrocyte production. Hypothyroid state leads to anaemia, since the blood cells are perhaps the most rapidly multiplying among all the cells in the body and a lack of thyroxine, the metabolic stimulant, is readily manifested as anaemia on account of depression of cell division in the marrow.

The gonadal growth and the attainment of reproductive capability is dependent on thyroxine. Impotence, reduced fertility and amenorrhoea are symptoms of hypothyroidism. Galactopoiesis or maintenance of milk secretion in the lactating mother is due to the thyroid hormone.

Regulation of Thyroid secretion : The thyroid develops and secretes its hormone at the optimum level under the direct control of the pars distalis of the Pituitary through its hormone thyrotrophin or TSH. TSH profoundly influences all the stages of synthesis of thyroxine, each one of which will be slowed down markedly in its absence, thereby bringing about a hormonal deficiency. The earliest effect of administration of thyrotrophin is the proteolytic action on thyroglobulin raising the level of free hormone in blood.

The release of TSH itself from the pituitary gland is under dual control—namely, a negative feedback mechanism dependent on the blood level of thyroxine and the nervous control operating through the hypothalamus by means of its thyrotrophin releasing factor. The rise in thyroid secretion, on exposure to cold, is an example of such a nervous control.

Chemical analogues of Thyroxine: The acetic acid analogues of thyroxine and tri-iodothyronine are tetra-iodothyroacetic acid (tetrac) and tri-iodothyroacetic acid (triac) respectively. These have the same actions as the thyroid hormones but without any time lag in the onset of action. It is conjectured that the thyroid hormones may be converted to tetrac and triac before they exert their action.

Tests for assessing thyroid activity: Determination of BMR has been a time-honoured procedure in this regard. BMR is, to a lesser degree, dependent on the actions of other hormones like the glucocorticoids. The necessity to devise a test to assess only thyroid activity, led to the determination of protein bound iodine (PBI) in the plasma. This is taken to be a better and more dependable method of estimating thyroid activity. Normally, plasma contains about 4–8 μ gm of PBI in 100 cc. Changes in this content will reflect functional derangement of the thyroid.

The uptake of radioactive iodine by the gland can also be used to gauge thyroid activity. It will be low in hypothyroidism and high in hyperthyroidism.

Thyroxine is partly destroyed in the body and the remainder excreted in the bile after conjugation with glucuronic acid.

Conditions arising out of dysfunction of the thyroid gland: A deficiency of thyroid hormone brings about cretinism in children and myxedema in adults. In the childhood condition, the retardation of growth, both physical and mental, is a marked feature which is absent in myxedema, the adult condition. A cretin is known for the marked delay in growth and attainment of the different stages leading on to adulthood. In fact, he may never become a full-blown adult. The skeleton, instead of showing

increased growth vertically, shows a broadening sideways giving a stocky appearance to the body. The head remains large in relation to the body, as in a child. The face is puffy owing to accumulation of protein-rich fluid under the skin. The so-called myxedematous tissue contains mucopolysaccharides. The tongue is enlarged (macroglossia) and may be seen protruding from the mouth which is too small to contain it completely. Scalp hair is very sparse and the skin is dry and devoid of sweat secretion and on this account is compared to the skin of a toad. The abdomen is prominent (pot belly). The gonads (sex organs) are very poorly developed and the individual may never become a sexually mature adult. The BMR is low. There is anaemia with raised blood cholesterol level. The intelligence quotient is low and the mental age is that of a child, even though the actual (chronological) age may be much more.

Myxedema: This has also been known as Gull's disease. The symptoms of hypothyroid state may manifest themselves for the first time in adulthood after full growth has occurred. The intelligence is not appreciably affected though there is a noticeable lethargy, both physical and mental. The skin exhibits the same abnormalities as described under cretinism. Amenorrhoea in women and impotence in men are features of depressed sex activity. The face has a puffy and swollen appearance. B.M.R. is low with fall in PBI. Blood cholesterol level is raised. The incidence of myxedema is higher in women than in men. Bradycardia with low voltage E.C.G. are abnormalities as regards the heart. The individual is very sensitive to low external temperatures on account of the absence of a suitable compensatory metabolic response.

Goitre: This term simply denotes a swelling or enlargement of the thyroid gland, associated with hypo or even normal or hyper function of the gland. People living in mountainous regions of Alps & Himalayas are subjected to iodine deficiency in diet and hence goitre is common among them (endemic goitre).

Hyperthyroidism: This condition may exist sometimes in association with the condition of exophthalmos, when it is known as Grave's disease or Exophthalmic goitre. A high B.M.R with

generalised bodily wasting are the characteristic features of this condition. Tachycardia with increased cardiac output and a raised B. P are invariably seen. The individual has an anxious expression. There may be hypermotility of the alimentary canal with increased appetite. Protein catabolism leads to wasting in spite of increased food intake. Tendon jerks are very brisk and fine tremors, especially of the small muscles of the hand, are seen. The patient cannot tolerate a rise in environmental temperature. The skin is warm and moist. Calcium excretion may be increased in the urine, leading on to rarefaction of bones.

Exophthalmos ; It is a forward displacement of the eyeball with associated widening of the palpebral fissure. Certain well-known clinical signs have been described in this regard. The underlying cause for this condition seems to be an accumulation of fat and fluid in the retro-bulbar space, possibly with some enlargement of the lachrymal glands. The degree of exophthalmus can be measured by a device known as exophthalmometer. Though weakening of muscles may be seen, yet this by itself may not be the cause of exophthalmos. The thyroid hormones were originally incriminated in this regard, but thyroidectomy actually aggravates this condition and administration of excess thyroid hormone does not produce this condition. Since exophthalmos does not occur in all cases of thyrotoxicosis, T.S.H. may not be the causative agent. A special causative factor (for exophthalmos) termed exophthalmos-producing substance (E.P.S.) is believed to be elaborated by the Pituitary gland. In addition, since there is apparently a failure of the normal negative feedback mechanism existing between thyroxine & T.S.H., it is reasonable to postulate that an abnormal and long acting thyroid stimulator (LATS) may take the role of the normal T.S.H. in hyperthyroidism.

A hypercalcemic factor named thyrocalcitonin has been isolated from thyroid tissue. Recent work indicates that certain specialised cells outside the thyroid acini proper, which are called C cells or ultimobronchial tissue may be responsible for its elaboration. The relationship between this factor and a similar factor in the parathyroid gland is yet to be worked out.

THE PARATHYROID GLANDS

The existence of this gland was suspected when fatalities occurred after thyroidectomy. Usually, two pairs of parathyroid glands are usually seen in close relation to the upper and lower poles of the thyroid lobes. Occasionally, the gland may be found near the thymus. The two pairs are derived from the third and fourth visceral clefts. The gland typically consists of cords or clumps of cells with wide vascular spaces in between. At birth, only one type of cell, namely—the chief cell with no granular cytoplasm and pale staining nucleus, is seen. This cell is the only secretory cell. About the time of puberty, a second type of cell, oxyntic or eosinophil cell, makes its appearance. Probably, the latter is a senile, functionless form of the chief cell.

Originally, the crude extract of the gland was known as Parathormone which name now passes off for the hormone of the gland. Parathormone is a hypercalcemic agent and when administered by injection (it is a polypeptide of M. W. 8500 – inactivated by digestive enzymes), a rise in plasma calcium level is the effect seen. This is believed to be brought about by one or more of the following modes of action :

- a) Originally, the primary site of action was believed to be the renal tubule. An increase in phosphate excretion occurred initially and this led to diminution of the ionic product of Ca^{++} & PO_4^{---} [$(\text{Ca}^{++}) \times (\text{Po}^{---}) = \text{a constant}$]. In order to restore the value of this product to the original figure, calcium is abstracted from the bones as a secondary effect. Thus, a rise in plasma calcium level occurs. This view was put forward by Albright and others.
- b) The primary site of action may also be the bone tissue, as seen from Barnicot's studies. When the gland was grafted to the skull bone of a rat and maintained in tissue culture, the bone was found to be eroded in the region of contact with the gland. This has been confirmed in experiments in vivo. Parathormone may bring about dissolution of bones by stimulating osteoclastic activity. The bone destroying cells are thought to release certain

organic acids, like citric acid which bring about the dissolution of bone and the liberation of calcium salts which find their way into the blood stream. Thus, hypercalcemia results.

The present position is that both mechanisms may operate in bringing about hypercalcemia.

Parathormone seems to also promote calcium absorption from the gut, as a subsidiary action.

The activity of the parathyroid gland does not depend on any pituitary hormone. The gland does not atrophy after hypophysectomy. The only controlling factor seems to be the level of calcium ions in blood. A fall provokes the secretion of parathormone while a rise inhibits it.

Calcitonin: Hypercalcemia produced after an administration of calcium salts intravenously, was set right more rapidly when parathyroid was intact than after parathyroidectomy. A hypocalcaemic factor seems to be responsible for this and it has been named calcitonin. This second factor may provide a fine adjustment in the maintenance of calcium level. (See also under 'Thyroid')

Tetany: This is a descriptive term for a hyperexcitable state of nerves and muscles in the body, resulting from a lowering of plasma level of ionised calcium. Tetany can also be brought about by a number of conditions other than hypoparathyroidism, such as alkalosis. But the actual causative factor is a fall in calcium content below the normal range of 9–11 mgms % in plasma. When the fall is by only a few mg., the symptoms can be unmasked by reducing the arterial blood supply to a limb as by a blood pressure cuff. Such a mild manifestation of a calcium deficiency is called latent tetany. When the fall in calcium level is greater, the term frank tetany is applied. There are a number of well-known clinical signs in this condition.

- 1) *Carpopedal spasm*: The arms and the legs are held in particular attitudes — the upper limb is adducted at the shoulder, flexed at the elbow and wrist and the thumb is

opposed to the extended fingers which are flexed to be at a right angle to the palm. Such an attitude of the hand compared to that of the obstetrician's (accoucheur's) hand in preparation for a gynaecological examination. In the case of the leg, extension of all joints occurs, the limb resembling that of a ballet dancer.

In latent tetany, the peculiar position of the hand can be assumed when the blood supply to the arm is arrested by inflating the cuff placed around the arm. This is *Trousseau's sign*.

- 2) *Chvostek's sign*: Tapping the facial nerve at the angle of the lower jaw brings about twitching of the facial muscles on the stimulated side.
- 3) *Laryngismus Stridulus*: The laryngeal muscles go into spasmodic contraction after a prior inspiratory effort. Air is trapped in the lungs due to the closure of the glottis. After an interval, the spasm is suddenly relieved and on the glottis opening out, the air in the lungs escapes out with a peculiar crowing sound.
- 4) *Erbs sign*: Increased sensitivity of muscles to galvanic stimulation.

Tetany can be dramatically alleviated by administering easily ionisable calcium salts like CaCl_2 (5%) solution given intravenously. As a long range measure, administration of parathormone and vitamin D to increase intestinal calcium absorption, can be done. The underlying cause, if it is other than hypoparathyroidism, will have to be treated. A synthetic Vitamin D analogue AT-10 or dihydrotachysterol has been used.

Hyperparathyroidism: Tumours of the parathyroid gland give rise to secretion of excess amounts of hormone. A persistently elevated plasma calcium level associated with generalized rarefaction of bones is the important feature in this condition. Stone formation in the kidney and urinary tract may also be seen. It is possible that the heart action may also be affected by a raised calcium level.

In a special variant of this condition, multiple cysts are seen in bones, when it is called Von Recklinghausen's disease. (Osteitis Fibrosa Cystica). Spontaneous fractures of bones are a logical consequence of such a condition. Treatment consists in removing the tumour tissue,

ADRENAL CORTEX

The term adrenal gland is to be preferred to supra-renal gland, in view of the possibility of extra glandular tissue being found away from the kidney. This gland is functionally not related to the adrenal medulla which it encloses, and embryologically it has a different origin. The cortex is developed from mesodermal tissue, namely—the coelomic epithelium covering the Wolffian body. The sex glands, ovary and testis, also arise from the same tissue and this explains the common steroid structure of cortical and sex hormones. There are no secretory nerves to the cells of adrenal cortex. It is larger in women who have borne children. *Histology*: Inside a fibrous capsule there are three distinct histological zones from without inwards. They are 1) Zona glomerulosa 2) Zona fasciculata 3) Zona reticularis. The outermost layer consists of polyhedral cells rather with indistinct margins containing small amounts of glycogen and arranged in the form of arches or circular or ovoid masses. The middle zone has again polyhedral cells disposed in columns or cords, running at right angles to the surface of the gland. These cells are very rich in lipid material — cholesterol and its esters which could be stained by the use of Sudan III and other fat stains. Ordinary histological techniques cause the dissolving out of this fatty material because of the use of alcohol. The fat stores are considered to be the source material for the synthesis of hormones. Vitamin C is also stored in the adrenal cortex, though its exact significance is not yet understood. It has as yet no known role in hormonal synthesis. On stimulation by ACTH, both lipid material and Vitamin C are depleted.

The inner zone consists of cells running in columns and forming a network and hence its name.

After hypophysectomy, Z. fasciculata and Z. reticularis are seen to atrophy, leaving Z. glomerulosa unaffected. From this it

is concluded that the Z. glomerulosa is not under pituitary control. Further, in cases of anterior pituitary failure, electrolyte disturbance is almost minimal. The conclusion to be drawn from this finding is that the Z-glomerulosa elaborates the mineralocorticoids responsible for maintaining electrolyte stability of the extracellular fluid. The inner zones synthesize glucocorticoids and sex steroids.

Chemistry of Adrenal Cortical Hormones :

Along with Vit. D, bile salts and cholesterol which is their precursor, the hormones of this gland belong to the large family of steroid compounds, all sharing a common nucleus namely — the cyclopentanoperhydrophenanthrene structure.

Cholesterol derived from either food or from active acetate CH_3Co — is the principal precursor for hormonal synthesis. Other pathways may possibly exist in hormonal synthesis. Cholesterol is itself converted to pregnenolone which in turn is changed to progesterone. Though this is a female sex hormone, yet its presence in the gland in appreciable amounts may only be incidental and it may be existing as an intermediate stage in hormonal synthesis. The glandular cell has the remarkable ability to introduce hydroxyl (OH) groups in sequence at the 17th, 21st and 11th carbon positions leading on to a harvest of the various hormones. A correlation between molecular structure and mode of action has been seen with regard to these hormones and is as follows :

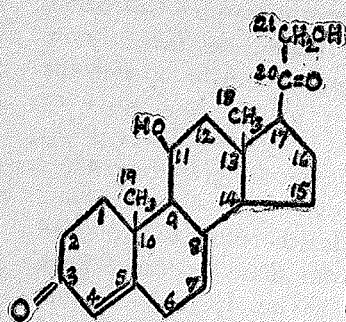
A ketone group at the 3rd carbon position and a double bond between the 4th and 5th carbon positions along with a hydroxyl group at the 21st carbon atom have to be present for a substance to qualify as a cortical hormone. Progesterone lacks the hydroxyl group at the 21C position. An OH or O_2 at the 11th carbon position confers the property of promoting muscular contraction and postponing fatigue on cortisol and corticosterone. This is lacking in desoxy-corticosterone which is hence devoid of the appropriate activity. A hydroxyl group at the 17th carbon position makes the hormone have a profound anti-inflammatory (antiphlogistic) action in addition to the anti-rheumatic

action. Cortisol is the only hormone with this action. Cortisone, though formerly considered as a natural hormone, is not now held to be so, though it is one of the thirty and odd steroids isolated from adrenal cortical tissue.

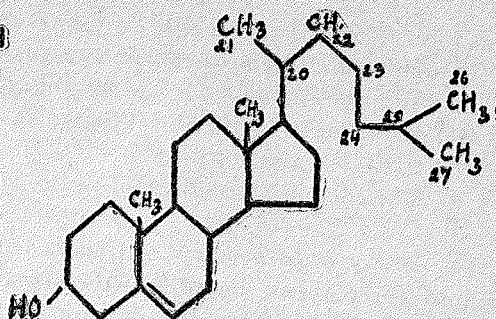
The chemical structures of the hormones are given on p.436.

Action of hormones : Adrenal cortical hormones are divided into three types, based on their predominant actions. Each variety of hormones in addition to having its main action, shares those of the others. The gluco-corticoids, cortisol and corticosterone influence glucose or carbohydrate metabolism profoundly. They are hyperglycemic in effect, promoting the entry of new glucose into blood, which is derived from non-carbohydrate sources like amino-acids (Neoglucogenesis). Gluco-corticoids, more than any other hormone, favour neoglucogenesis. Certain amino acids termed as glycogenic-glycine, cysteine, cystine, serine, are specially prone to be converted to glucose. In view of the much larger daily output of cortisol, in comparison with corticosterone, the former can be called as *the* glucocorticoid in the human species. Corticosterone lacks the anti-rheumatic and anti-inflammatory activity of cortisol. Its daily output is about 1/10th of that of cortisol—20 mgms. Cortisol and its closely related steroid, cortisone, are well known for their facilitating action on muscle performance. They are noted for their effect in postponing muscular fatigue by virtue of the keto or hydroxyl group at the 11th carbon position. The glucocorticoids have an inhibitory influence on the hexokinase reaction which starts off the metabolic breakdown of glucose. In this, they are opposed by insulin. Thus, glucocorticoids prevent cellular utilization of glucose, thereby preventing withdrawal of glucose from blood. Strangely, their action in promoting the deposition of glycogen in the liver tends to bring down blood sugar content. It is apparent that the other two actions overwhelm this effect, the nett change being a rise in blood sugar level.

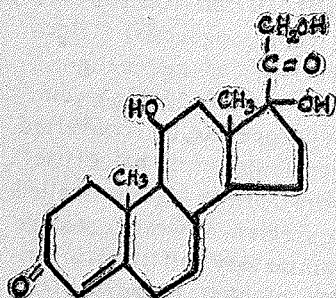
Mineralocorticoids : Aldosterone and desoxycorticosterone (DOC) belong to this group. Aldosterone, so called because of its aldehyde group at the 18th carbon position, was not



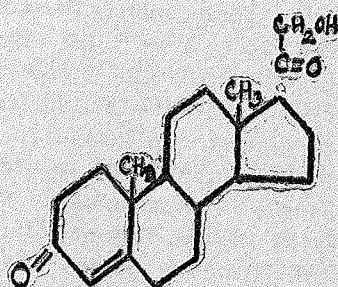
Corticosterone



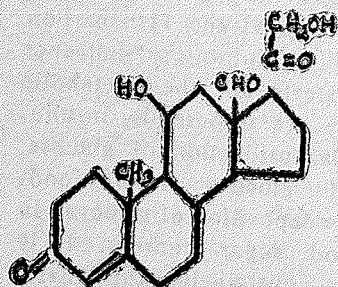
Cholesterol



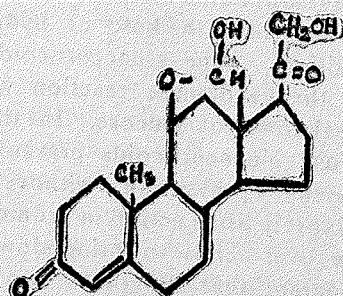
Cortisol (Compound F)



11-Deoxycorticosterone (DOC)



aldehyde form



hemiacetal form



Aldosterone

Fig. 31

discovered earlier, in view of its being a part of the amorphous residue left after other steroids had been extracted. It is about a 100 times as potent as DOC., as a mineralocorticoid. Its main action is to cause retention of sodium in the body and thereby its conservation. The main site of action is the renal tubule where re-absorption of sodium is favoured. Concomitant with this is the promotion of potassium excretion. The mineralocorticoids which are salt retaining hormones can act on all cell membranes in promoting sodium retention and potassium excretion. An example of such an action is seen in the case of the dwindling concentration of NaCl in sweat, as its secretion is prolonged when a subject is exposed for long periods to high environmental temperature. So also in profuse sweating consequent on maximal muscular effort. Here the action is on the sweat glands.

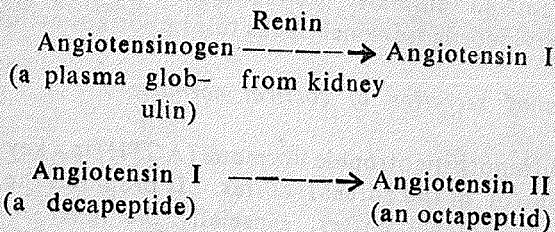
The glucocorticoids do have a salt retaining action. While the mineralocorticoids can also exhibit metabolic effects, yet in view of the very small amounts in which aldosterone (200 μ gms/day) is secreted, its action in this regard is negligible. The effects on electrolyte balance that can be ascribed to glucocorticoids is considerable because of the relatively much higher amounts in which they are released. The ability to sustain life in adrenalectomized animals, distinguishes aldosterone from the other mineralocorticoid which lacks this important action.

Regulation of secretion of cortical hormones:

The adrenocorticotrophic hormone (ACTH) is a key hormone in the control of the adrenal cortex. It promotes the development of the adrenal cortex, especially the inner zones. The elaboration of glucocorticoids is specifically influenced by ACTH which accelerates the conversion of cholesterol to pregnenolone in the presence of NADPH. The formation of this coenzyme itself is furthered by ACTH which indirectly favours it by causing the breakdown of ATP to 3' 5' adenosine monophosphate ester which itself brings about glycolytic changes leading on to the formation of the co-enzyme referred to above. ACTH does not seem to feature in the regulation of mineralocorticoid secretion as far as is known now.

The release of ACTH from the adenohypophysis is itself under a dual regulatory mechanism like other pituitary 'trophic' hormones. It is subject to a negative feed-back influence operating through rise in blood levels of glucocorticoids. Nervous factors also exert a controlling action by bringing about a release of a neuro-humor, corticotrophin-releasing factor in the hypothalamus which, after being conveyed to the anterior pituitary gland by way of the portal vessels, causes the gland to put forth ACTH.

The secretion of aldosterone is possibly influenced by more than one regulatory mechanism. It has been postulated that there are some volume receptors in the subdiaphragmatic part of the inferior vena cava and also in the walls of the cardiac chambers. These are excited by an expansion of the extracellular fluid compartment or a fall in the level of ionic sodium in the extracellular fluid. The nerve impulses generated by the volume receptors stimulate a diencephalic centre in the region of the pineal body which releases a humoral factor—the glomerulotrophin—to act on the zona glomerulosa, causing the release of aldosterone. Another mode of control is by the stimulation of the aldosterone secreting cells by angiotensin II whose origin is as follows:



The physiological role that can be attributed to adrenal cortical sex hormones, is rather obscure. If at all, the persistence of libido after castration is attributed to these hormones.

Disorders of adrenal function:

A deficiency of cortical hormones leads to three types of conditions.

(1) Total cortical deficiency, either acute or chronic.

a) In subjects exposed to a sudden deficiency of all the cortical hormones, characteristic symptoms (adrenal crisis) are seen. Profound prostration, marked muscular weakness and arterial hypotension, are important symptoms which reflect a lack of gluco and mineralo corticoids. Such a condition may occur when steroid therapy is stopped all of a sudden during treatment of certain diseases. The necessity for the gradual tapering off, of the dosage is the lesson to be learnt from this.

b) Addison's disease results from chronic adrenocortical deficiency as occurs after a tuberculous destruction of the gland, perhaps with greater incidence in the past than now. The cardinal symptoms of this being, a completely disabling muscular weakness, accounting for the prostrate condition of the patient. Easy fatiguability is a manifestation of a milder form. A low arterial blood pressure accompanied by hyperkalemia, hyponatremia with accumulation of non-protein nitrogenous substances, are changes seen. Muscular weakness seems to be the result of not only deranged carbohydrate metabolism but also electrolyte imbalance. In the case of primates, pigmentation of skin and mucous membranes known as bronzing, is a unique feature. This discolouration is specially seen in the palmar aspects of hands, face and in the buccal mucosa. This is explained on the basis of a side action of ACTH (melanophore spreading action) which in the absence of a negative feedback inhibitory regulation, occurs in a high titre in blood. The medulla also undergoes destruction in this condition and theoretically at least, much more melanin may be synthesized as a result of diversion of tyrosine - adrenaline pathway.

(2) *Anterior pituitary failure*: When there is failure on the part of the pituitary gland to secrete its hormones, especially ACTH, symptoms already described above, may come on due to lack of stimulation of the adrenal cortex. However, effects of electrolyte disturbances will not be seen, as the secretion of mineralocorticoids will in no way be diminished.

- (3) Precocious virilism may be seen in children of both sexes owing to a congenital absence of one or more enzymes involved in hormonal synthesis. In one type of enzyme defect, the conversion of progesterone to 17 OH, 11 desoxycorticosterone is blocked, leading to the accumulation of the former product which is diverted to form androgens, on a much larger scale than normally.

The child exhibits symptoms of virilisation. In the case of a young boy, growth stops, the bones becoming thicker and heavier. Secondary sex characters like facial and body hair will appear much earlier than puberty. The genital organs are precociously enlarged. The body itself assumes a stocky build. This is picturesquely called "Infant Hercules" type or "burly brewer's drayman". In female children, masculine external genitalia may be seen even at birth, giving rise to pseudo-hermaphroditism. In the second type of enzyme defect, because of the failure to carry on the conversion of 17 hydroxy 11 desoxycorticosterone to the stage of cortisol, in addition to the symptoms of precocious sexual development, there will be symptoms of excess activity of mineralocorticoids.

Cushing's Syndrome: Release of cortisol in larger amounts than usual, either secondarily to pituitary overactivity or primarily to adrenal hypersecretion, will cause this well-known condition. The individual usually is of excessive weight, mainly confined to the trunk, fat having been re-distributed from the limbs which appear wasted. The face takes on a round contour (moon face). The mouth (fish mouth) and the gap between the eyelids appear narrower. Purplish striae occur on the abdomen and limbs due to destruction of the protein matrix of the connective tissue under the skin. Osteoporosis and thinning of bones with attendant loss of calcium in urine are some features seen. Hyperglycemia and glycosuria result from deranged carbohydrate metabolism (adrenal diabetes). Abnormal hairiness of the body (hirsutism) results from excess androgen activity. Mild disturbances in the electrolyte balance may be seen. Impotence and amenorrhoea

are symptoms caused by suppression of sexual functions. Mental changes ranging from depression to euphoria (abnormal sense of well being) and even mania may be seen. Wounds which are liable to get infected are very slow in healing.

Adrenogenital Syndrome: This is invariably due to an adrenal tumour. There is a strong tendency for the development of secondary characteristics of the opposite sex. Adult women become masculinized with profuse growth of facial and body hair, with the male pattern of distribution. Diabetes mellitus may also occur. (Diabetes of bearded women). The 17-ketosteroid excretion may be increased, as in Cushing's syndrome. Feminine sexual functions are suppressed. Surgical removal of the tumour sets forth a dramatic regression of the virilising changes. Femininising changes with enlargement of breasts are seen in men. Oestrogen output rises. Atrophy of testis and loss of libido are other features.

Hyperaldosteronism: In the primary form (Conn's syndrome), hypertension, hypernatremia, hypokalaemia and muscular weakness are some of the prominent features. There is no oedema. In the secondary type arising out of oedematous states like nephrosis, congestive failure and others, aldosterone is secreted in large amounts, as a response to water retention. This is perpetuated by the hormone, a vicious cycle being established.

Certain synthetic steroid hormones: Cortisone has been widely used in medicine in view of its anti-inflammatory and antirheumatic properties, in addition to its favourable action on muscle performance. Other synthetic derivatives specially developed to exert only one or two actions, of natural steroids have also been developed. Prednisone is one such well-known agent. Spirolactone has been used to suppress mineralocorticoid activity in aldosteronism. Fludrocortisone has a pronounced sodium retaining activity.

Tests to assess adrenal function: The administration of ACTH to a subject, brings about a fall in the circulating blood eosinophil count in about four hours. In deficiency

states, the eosinopenic response is diminished or absent. While there are other tests, the determination of the daily output of 17 ketosteroids (17 oxysteroids) has also come into vogue. The hydroxysteroids are converted into 17 oxysteroids in the course of metabolic degradation of these hormones. In normal subjects, the daily excretion amounts to 8 mgms in the case of males, and 4—5 mgms in the case of females. The difference between the two sexes is due to the testicular contribution in the case of the male. The 17 ketosteroids referred to, are androsterone, 11 dehydro epiandrosterone and 11 hydroxy epiandrosterone.

STRESS AND THE ADRENAL CORTEX

Stress is a general term referable to anyone of a number of factors which call forth a stereotyped or a standardised response from the body by way of mainly an augmented glucocorticoid secretion. Infections, exposure to cold or excessive heat, strong emotions, muscular exercise, violent games and administration of drugs, are some of the well known forms of stress. According to Hans Selye, the body puts out a response which is composed of the same elements under stress of any origin. It was his opinion that some diseases (if not all) that the body fell a prey to, resulted from a failure of the proper physiological adjustments when confronted by stress. Most often, the subject gets over the harmful effects of stress by adaptation to the new conditions caused by stress. The symptom complex indicative of adaptation was designated by Selye as the General Adaptation Syndrome (G.A.S.). Diseases, according to this author, arose as a result of maladaptation or failure of adaptation. Selye described three stages in the process of adaptation. Whatever may be the actual form of stress, the manifestations of adaptation are the same, in other words, nonspecific and generalised or systemic.

- 1) The alarm reaction (Stage of shock): When the body is confronted by stress, initially certain changes occur and these are indicative of the unpreparedness of the body. Symptoms of nervous and vascular depression (hypotension), and fall in body temperature are seen.

- 2) In the second stage, the body mobilises its defences as a response to stress in order to overcome it. Cortical hormones (glucocorticoids) are poured into circulation and the body resistance to the disease process (stress) is built up. This phase is also known as the stage of countershock. It has been mentioned before that glucocorticoids suppress the tissue responses to inflammation. The harmful effects of stressor agents tend to be suppressed so as to prevent the onset of a disease process. Most often, Selye opined, the second stage brings to a close the effects of stress and no sequel in the form of actual disease follows. In other words, successful adaptation to stress has taken place.
- 3) The stage of exhaustion — Sometimes, the adaptational changes cannot be maintained in the face of increasing or continuing stress. The adrenal cortex cannot be whipped up any more to sustain the bodily resistance to stress. The individual's defences buckle under the overwhelming onslaught of the noxious stressor stimuli. Pathological processes gain the upper hand and actual disease manifests itself.

It is of interest to note that adaptation or maladaptation, as Selye conceived, resulted from an imbalance between antiphlogistic (glucocorticoids — anti inflammatory) and phlogistic hormones (mineralocorticoid, 11 desoxy hormones — proinflammatory). If the former predominate, adaptation occurs. In the opposite case, maladaptation or unmasking of the disease process ensues, due to adrenal exhaustion.

In view of the ignorance that still prevails with regard to the causative factors in the aetiology of the so called diseases of maladaptation, it is not possible to consider Selye's ideas as having been confirmed.

THE ADRENAL MEDULLA

This gland is sequestered inside the adrenal cortex with which it has no apparent functional relationship. Clumps of ovoid and columnar cells aggregating around blood vessels,

form the cellular elements of the glands. Their embryological origin is referred to under Autonomic Nervous System. The cells of this gland stain bluish green with ferric chloride. This reaction is due to adrenaline in the cells. Chromic acid also can be used to stain the cells which present brown 'chromaffin' granules. The brownish colouration is due to the oxidation of adrenaline and related substances. Adrenaline can be revealed as granules in the cells by osmic acid fixation also. The cells themselves are of two kinds, each synthesizing a different hormone, either adrenaline or noradrenaline. The cell type that is responsible for adrenaline, obviously has a methylating enzyme (see below for the chemical pathway) which the other probably lacks. Adrenaline accounts for 80 % of the output of the gland, the remainder being noradrenaline. The hypothalamus which regulates the release of adrenaline and noradrenaline is said to possess two kinds of cells, each concerned with the release of one of the medullary hormones—either adrenaline or noradrenaline. Thus, there seems to be a dichotomy or two-fold division from the hypothalamus through the sympathetic fibres (splanchnic nerves) to the medulla. Asphyxia and carotid artery occlusion are said to favour noradrenaline secretion while stimulation of a sensory nerve and fall in blood glucose level elicit exclusively adrenaline secretion. The hormones of the adrenal medulla are usually known as catechol- $\text{C}_6\text{H}_4(\text{OH})_2$ - amines though they are not the only catecholamines.

Synthesis of medullary hormones: The aromatic amino acid, tyrosine, is the starting point for the stepwise changes leading to the formation of the two hormones. (See fig. 32)

Fate of Medullary Hormones: Endogenous and exogenous medullary hormones introduced into the body have a very short lived action, suggesting their rapid inactivation. A major portion of the dose of either hormone administered, is methylated (at 3 C position) to form either metanephrine or normetanephrine and much of this is excreted in urine as such. The greater part of the remainder is converted to 3-methoxy, 4-hydroxy mandelic acid by the action of monoamine oxidase and also excreted in urine. Smaller amounts of the hormones are conjugated with glucuronic acid and eliminated in the urine. When a freshly

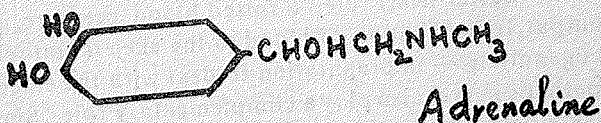
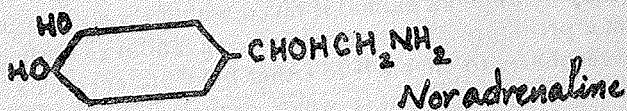
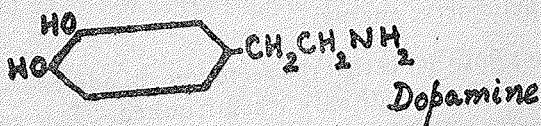
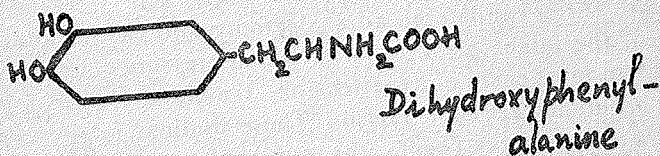
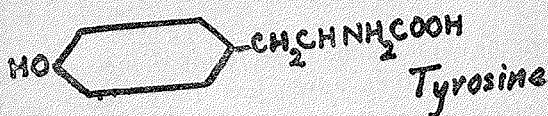
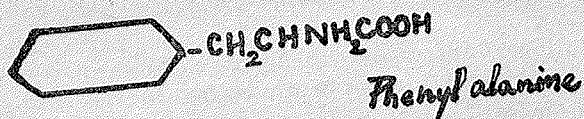


Fig 32. Derivation of Medullary hormones

made solution of adrenaline is exposed to atmospheric oxygen in the presence of light, it turns brown owing to the formation of adrenochrome whose pharmacological actions are antagonistic to those of adrenaline.

The functional significance of medullary hormones: This question involves the actual mode of secretion of these hormones. A view (now refuted) was that adrenaline (also noradrenaline) was constantly released and it was necessary to maintain heart rate, blood pressure etc. at normal levels. In the absence of these hormones, the blood pressure and heart rate were assumed to fall. After unilateral adrenalectomy and piecemeal destruction of the intact gland, a fall in blood pressure did not follow. Also, in most cases of hypertension, the blood levels of medullary hormones are not raised. These findings falsify what was known as the Tonus Theory, the term implying that the hormones are necessary for sustaining the tone or the state of excitability of the sympathetic nerve endings.

The present position is that the secretion of adrenaline and noradrenaline seems to occur only when required. This concept goes by the name 'the emergency theory', put forward by Cannon. The medulla releases its hormones only in a state of emergency — when an animal is faced with a threat to its life, as from a predator. The hormones bring about suitable physiological responses to enable it to either fight its enemy or indulge in flight to escape. Fright is what provokes the secretion of the hormones. Whether fight or flight is resorted to, adrenaline and noradrenaline evoke the appropriate cardio-vascular adjustments — faster heart rate, a raised blood pressure, greater cardiac output, redistribution of blood to the skeletal muscles and liver glycogenolysis — in preparation to deal with the emergency. The sympathetic nerves also play a complementary role. Similarly, anger, severe pain, exposure to cold, and asphyxia can set off an intense secretory response of the medulla.

The various factors which are excitants for adrenal medullary secretion act through the hypothalamus (posterior nuclei) which sends down a barrage of impulses through the descending pathways in the brain stem and the cord to excite the splanchnic nerves and thereby the adrenal medulla itself.

A large number of pharmacological actions of adrenaline and noradrenaline have been studied and are described below.

- 1a) When adrenaline is given by injection to an experimental animal under an anaesthetic, a rise in the blood pressure is seen, both systolic and diastolic altering in the same direction. Reflex bradycardia follows the rise in B. P. which is short-lived. The rise in B. P. is due to an increase in the cardiac output. The effects on the blood vessels are vasoconstriction in the cutaneous and splanchnic vessels with vasodilatation of the arteries in the muscles and the coronary vessels. Even the venous and capillary vessels respond to adrenaline, by constriction.
- b) Acting on the isolated perfused heart—amphibian and mammalian—, adrenaline causes augmentation (increase in the force of contraction) and acceleration (rise in rate).
- 2a) In man, a moderate dose of adrenaline given intravenously, produces a rise in the blood pressure—see 1.(a), with reflex slowing of the heart as a secondary effect.
- b) In man, a slow intravenous transfusion of adrenaline causes rise in systolic but a fall in diastolic pressure with mean pressure not affected. Hence there is no reflex bradycardia. Rapid heart rate persists for some time, as also greater cardiac output with fall in peripheral resistance (fall in diastolic)

When noradrenaline is given intravenously as a transfusion, both the systolic and the diastolic pressures rise and hence there is reflex slowing of the heart. Peripheral resistance is increased as noradrenaline is a constrictor for all vessels.

Since peripheral resistance falls with adrenaline administration, it is called an overall vasodilator, while noradrenaline is an overall vasoconstrictor. Adrenaline has no action on the cerebral and pulmonary vessels. The vasodilator action of adrenaline in the muscles is best demonstrated in a skinned limb whose volume increases. When covered with skin this

effect is not seen. Noradrenaline has less effect on cutaneous vessels as well as those under mucous membranes, than adrenaline. The contraction of the arrectores pili—piloerection (stimulation of the small muscles of the skin) is an associated effect giving rise to goose flesh appearance. Adrenaline has no effect on human sweat secretion. Blanching of skin is more with adrenaline. The effect of noradrenaline on veins is best seen in states of shock, when, by means of venous constriction, venous return to the heart is increased raising the cardiac output.

- 3) Adrenaline, in large doses, produces apnoea as an indirect effect. The rise in blood pressure, reflexly brings about this effect through the pressoreceptor reflexes of the carotid sinus and the aortic arch. If, however, the rise in blood pressure is avoided, stimulation of respiration results. Adrenaline and noradrenaline in small doses given intravenously bring about an increase in rate and depth of respiration by a direct action on the respiratory centre.

A therapeutic use of adrenaline (not noradrenaline) is in relieving bronchospasm in asthma. The effect is quite impressive. The bronchioles relax and expiration which was difficult is now facilitated. The secretions of the bronchial passages are also minimised and because of an action on the blood vessels, shrinkage of the mucous membrane and thus, further widening of the passages also result.

- 4) In the eye, adrenaline enlarges the pupil by an action on the dilator muscle. In hyperthyroid states, the action of adrenaline is potentiated. Retraction of the upper eyelid and protrusion of the eye balls are other effects. In animals, the nictitating membrane is retracted.

- 5) While in general, adrenaline inhibits the walls of the alimentary canal and excites the sphincters, yet these actions seem to depend on the existing muscle tone. Splenic contraction is a marked effect in animals because of plain muscle fibres in the splenic capsule. It is not so in man in whom a diminution in splenic size is not seen.

- 6) Relaxation of the detrussor of the urinary bladder, closing of the internal sphincter and contraction of the trigone are the effects of adrenaline. Ureters are made to contract narrowing their lumen.
- 7) Adrenaline inhibits the human uterus in late pregnancy as well as in labour and in puerperium. Noradrenaline excites the muscle. Both hormones provoke contraction of the isolated human uterus taken out of the body.
- 8) Adrenaline hastens the coagulation processes,
- 9) Fatigue is abolished and more blood flow to skeletal muscle occurs as a result of vasodilatation. These are beneficial effects of adrenaline.
- 10) Small doses of adrenaline effect vasoconstriction of the efferent arteriole, of the glomerulus in the kidney resulting in greater urinary output. With large doses, both afferent and efferent arteries are affected and urine output is diminished. Noradrenaline has similar effects.

While adrenaline and noradrenaline exert similar effects at many sites yet they differ in some respects.

- 1) Adrenaline is a selective vasoconstrictor. It has a vasodilator action on coronary vessels and those of skeletal muscles. Nor-adrenaline is a constrictor to all vessels.
- 2) Adrenaline has certain metabolic actions which are not shared with noradrenaline. Adrenaline promotes glycogenolysis in the liver and noradrenaline has very little effect in this regard. Adrenaline activates the enzymes involved in the breakdown of glycogen as well as the phosphatases which spilt off the glucose finally. Adrenaline stimulates breakdown of muscle glycogen also, but in view of the lack of glucose-6-phosphatase, the glucose of the muscle is not set free to enter the blood stream. It is utilised in the muscle fibre itself.

Ahlquist put forward a hypothesis to explain the differences in actions of adrenaline and noradrenaline. The adrenergic receptors found in the various effector tissues are of two kinds. Those responsible for vasoconstriction, cardiac excitability and contractility, uterine contraction, relaxation of the walls of the alimentary canal, glycogen breakdown, among others, are termed as alpha receptors. Those concerned with vasodilatation, cardio acceleration, bronchial relaxation etc. are called Beta receptors. Plain muscle fibres may have both receptors. Noradrenaline is taken to act on alpha receptors only but adrenaline unites with both alpha and beta receptors and this accounts for its different effects at different sites. Adrenaline is more effective than nor-adrenaline even with regard to the alpha receptors. Isoproterenol is more potent in the case of beta receptors, than adrenaline. Ahlquist's views help to explain the pharmacological effects of the catechol amines.

Dale's reversal: Sir Henry Dale showed that adrenaline raises the blood pressure because of the increased cardiac output even though the peripheral resistance was lowered. But if ergotamine is administered prior to adrenaline, a fall in blood pressure results. This was explained as being solely due to vasodilatation in the muscular vessels uncomplicated by vasoconstriction in cutaneous and splanchnic vessels. In the light of Ahlquist's ideas, it can now be taken that Dale's reversal is due to the inactivation or blocking of the alpha receptors by ergotamine, the beta receptors only being left to respond to adrenaline.

(For adrenaline antagonists, see Autonomic Nervous System).

Certain recent studies have indicated that in aggressive animals, eg.—cat family, the medulla has more of noradrenaline, while the rabbit and such timid creatures, have more of adrenaline in their glands. Thus, these hormones seem to determine the behaviour of an animal—aggressiveness in the predators and timidity and defensive reactions in the small animals.

PANCREAS AS AN ENDOCRINE GLAND

The role of the pancreas in digestion has already been referred to. Dispersed among the alveoli or the acini (secreting the digestive juice) are the islets of Langerhans which have been shown to elaborate the internal secretions of the pancreas. In the human pancreas, the islets are made of four types of cells — α , β , γ & δ . The α cells have to be fixed with alcoholic solutions and the β cells with aqueous solutions for staining. The β cells which are seen at the periphery of the islet tissue are responsible for the secretion of insulin. The α cells are thought to be the source of glucagon, the other hormone of the gland. The functions of the γ and δ cells are not known.

Insulin: The role of the pancreas in carbohydrate metabolism was indicated by Von Mering and Minkowski in 1889, who, by removal of the pancreas in the dog, produced a state akin to human diabetes. It was subsequently shown by others that grafting of pancreatic tissue abolished the diabetic state. Allen, in 1913, observed diabetes in dogs which underwent partial pancreatectomy and were fed with high carbohydrate diet. The β cells of the islets were seen to have degenerated as a result. All this preliminary work implicated the pancreas or the islet tissue and especially the β cells in carbohydrate metabolism.

Banting and Best, at Toronto in 1921, made the remarkable discovery of insulin which won for Banting the Nobel prize that he was made to share with Professor Mcleod in whose laboratory he happened to work.

Banting and Best tied the pancreatic duct in the dog. Due to the pressure built up in the ducts and the alveoli by the constant secretion of the pancreatic juice, the acinar tissue suffered atrophy and was absorbed leaving behind a thin piece of tissue containing only the islets. Diabetes did not result as a consequence, but when the islet tissue was also removed, diabetes followed, conclusively demonstrating its role in secreting some as yet unknown anti-diabetic factor.

Extracts of the islet tissue proved effective in curing human and animal diabetes.

Further confirmation that the β cells were the source of the anti-diabetic principle was provided by the undermentioned evidence:

- 1) The administration of alloxan, a drug, produced degenerative changes in the β cells and thereby a diabetic state.
- 2) Repeated injection of extracts of the anterior pituitary gland brought about degenerative changes in the β cells.
- 3) Post-mortem examination of the pancreases of persons known to be diabetics revealed degeneration in the β cells.

Mayer named the anti-diabetic hormone of the pancreas, insulin (insular – pertaining to an island or isle). By 1930, insulin was isolated from the pancreatic tissue. Later, Sanger elucidated the chemical structure of insulin which is a protein with a molecular weight of 48,000 (in solution). It could be prepared in a crystalline state in which it existed in smaller molecular units of M.W 12,000 which itself was a polymer of sub-units of M.W 6000 each. The sub-unit, built of 51 aminoacid residues was found to comprise two chains of amino acids, linked together by disulphide bonds ($-S-S-$). Sulphur containing amino acids—cystine and cysteine, as well as the element zinc, were seen to occur in the molecular structure. Crystalline insulin is soluble in water (soluble or simple insulin) and has to be administered only parenterally and not orally on account of its protein nature. Certain organs like the kidney, liver and muscle take up insulin from the blood in which it seems to be bound to the globulin fraction. Insulin is inactivated in the body by an enzyme, insulinase which splits off the two chains in the molecule.

Effects of insulin administration: After a single dose, a fall in glucose level of blood as well as in body fluids occurs,

commencing in about an hour, attaining a maximum effect in about 2-3 hours and slowly waning away in about six hours. The following metabolic changes are brought about and these are responsible for the hypoglycemic effect.

- 1) Promotion of the peripheral utilisation of glucose by the cells.
- 2) Prevention of neoglucogenesis - conversion of non-carbohydrate substances like amino acids, lactic acid and glycerol into glucose.
- 3) Promotion of deposition of glycogen in the liver, mainly and muscles and possibly other tissues too. In addition, it may oppose breakdown of liver glycogen.

Actions (1) and (3) bring about the withdrawal of glucose from blood and action (2) prevents addition of fresh glucose to the blood, with prolonged therapy with insulin as in diabetes.

The actions enumerated above are brought about in the ways described below.

The actions of insulin have been studied in the whole animal before and after pancreatectomy, in an eviscerated animal - liver, kidneys and the intestine having been removed to prevent absorption of glucose from the gut and to avoid excretion by the kidney. The liver is removed because it is the seat of action of enzymes and hormones, concerned with blood sugar regulation. Thirdly, isolated whole organs or slices (perfused) of tissues or organs (liver or muscle) have been used to study the influence of enzymes in the presence of insulin. The rat diaphragm muscle has been used to find about glucose uptake and formation of glycogen thereby.

Insulin appears to act at the cellular level in the following ways.

- 1) It facilitates the transport of glucose across the cell membrane into the cell interior. The cell membrane is almost

impermeable to glucose, in the absence of insulin. Glucose can enter the cell if the extracellular concentration is very high, but at the usual levels of glucose in the blood and extracellular fluid, very little will find its way into the cell, except with the aid of insulin. This action of insulin is its most important one in bringing about cellular oxidation of glucose. The oxidation of glucose to form carbon dioxide and water is initiated by insulin which promotes the action of the enzyme hexokinase which brings about the first reaction in glycolysis, viz – the phosphorylation of glucose to yield glucose-6 phosphate. It is this effect of insulin on the hexokinase enzyme that is antagonised by the diabetogenic hormone of the adenohypophysis and the glucocorticoids of adrenal cortex.

- 3) Insulin, in the presence of adequate amounts of glucose promotes the action of the phosphorylating and condensing enzymes which bring about deposition of liver and muscle glycogen.
- 4) The prevention of neoglucogenesis in the liver is another action.
- 5) Insulin accelerates the uptake of amino acids by the cell by increasing their transport across the cell membrane. Thus protein synthesis is facilitated, but in the absence of insulin it dwindles almost to nothing.
- 6) In diabetes one of the consequences of repeated insulin administration over prolonged periods is the gain in weight by the build-up of fat reserves. Insulin promotes the conversion of most of the ingested glucose into fatty acids and eventually into fat. Insulin reduces the rate of release of free fatty acids (FFA) from adipose tissue and enhances their re-esterification which otherwise (in the absence of insulin) would accumulate in the blood.

The interaction between the Growth hormone and Insulin: The role of the growth hormone in carbohydrate metabolism

was unmasked by Bernardo Houssay, the Argentinian Physiologist who (see under hypophysis) was awarded the Nobel prize. It was shown in the years following Houssay's work that the two hormones somatotrophin and insulin, though apparently antagonistic in their actions—one is diabetogenic and the other anti-diabetic—, strangely enough act in a synergistic manner in promoting growth. A pancreatectomised animal failed to grow even when growth hormone was administered. Likewise, a diet poor in carbohydrate prevented an animal's growth under the stimulus of somatotrophin. It is well known that an injection of growth hormone provokes a release of insulin. Repeated administration of the pituitary factor brings about exhaustion atrophy of the islets of Langerhans and in its wake, what is named as metahypophyseal diabetes which is a permanent condition. Hypophyseal diabetes which is induced by a single large dose of somatotrophin is a short lived condition which is terminated by a rebound secretion of insulin. The action of insulin in effecting amino acid transfer across the cell membrane may also logically be concerned with its synergism with the growth hormone, which is thought to increase the rate of protein synthesis in all the cells in the body as one of its growth promoting actions.

The Regulation of the secretion of insulin: The major mechanism controlling insulin output is by fluctuation in the blood sugar level. When there is hyperglycaemia (with content rising above the fasting level) the islets are stimulated and insulin is released so as to arrest further rise of glucose level and also to bring down the level. A fall in the sugar content of blood below the normal range will depress the activity of the β cells.

The role of the vagus which furnishes many fibres to the islet tissue is not very clear. Excitation of the vagus also increases the insulin output. It is now held that the vagal action results in a precise and finer control of insulin secretion brought about by a rise of blood glucose level.

Effects of hypoglycaemia: Symptoms appear with a sudden onset when there is a fall in the blood glucose level below 50 mg %.

There is a sensation of extreme exhaustion with a feeling of profound weakness and inability to even move the limbs. Anxiety coupled with excitability or irritability are the mental symptoms. Voluntary muscular control is impaired. Intense sweating is a prominent feature. Vasodilatation causes flushing of skin. On the other hand, blanching of skin causing pallor, may occur. If hypoglycaemia is not relieved, the condition may deteriorate, resulting in convulsions and unconsciousness (coma), terminating in death.

This clinical condition can result after over-enthusiastic insulin therapy in diabetes mellitus. Hyper-insulinism caused by a tumour of the islet tissue may also be responsible for hypoglycaemia.

The most dramatic recovery takes place with an intravenous injection of glucose in aqueous solution. Even a deeply comatose person regains consciousness very soon and sits up as if nothing has happened. In well-nourished individuals (with large glycogen stores in the liver), adrenaline can be administered to effect a recovery by a rapid glycogenolysis in the liver.

While hypoglycaemia, if unchecked, has a fatal sequel, hyperglycaemia — a rise in blood sugar level — by itself does not have adverse effects. The harmful features of diabetes mellitus are due to acidosis and ketosis.

Diabetes Mellitus: The basic cause of what has come to be known as the classical diabetes mellitus is a deficiency of insulin. But all cases which show symptoms of diabetes mellitus — hyperglycaemia and glycosuria — need not necessarily result from lack of insulin. Hyper-secretion of the somatotrophin (metahypophyseal diabetes — see under Pituitary Gland), glucocorticoids, thyroxine and glucagon, can give rise to a clinical picture of diabetes mellitus. Even so, an insufficiency of insulin brought on by exhaustion atrophy of the pancreatic islets, can still be held to be the underlying cause of diabetes mellitus.

It has however, to be mentioned that in some cases of diabetes mellitus resulting from total pancreatectomy and when there

is no other source of insulin, small doses or moderate doses of insulin were found to be sufficient to ward off the symptoms. On the other hand, high doses of insulin were required by patients who had spontaneous or idiopathic diabetes, even though these persons presumably had some active islet tissue in the body. Certain studies involving hepatectomy showed that in the absence of the liver, even in the diabetic dogs, hypoglycemia occurred, leading to death. The liver seems to be partly responsible for the hyperglycemia of diabetes. Hitherto, insulin lack was assumed to be the sole cause for the high blood sugar level. In the ultimate analysis, while insulin lack is a major causative factor in diabetes mellitus, there appears to be in some cases, a derangement of the delicate balance underlying blood sugar level maintenance.

An animal which has been rendered diabetic permanently by repeated injections of anterior pituitary extracts or somatotrophin has been termed a 'Young' animal. Housay removed the pituitary gland in such an animal and the diabetic state was either ameliorated or abolished and such an animal which has undergone pancreatectomy (in effect) and hypophysectomy came to be known as a 'Housay' animal. Apparently, this preparation is normal though its blood sugar level can be easily disturbed by glucose administration when sudden hyperglycaemia results or in fasting conditions when the blood sugar content falls steeply.

The cardinal features of diabetes mellitus are :

- 1) Presence of reducing sugar (glucose) in the post-prandial urine, invariably.
- 2) A sustained high level of blood sugar and a higher than normal fasting blood sugar level.

While glycosuria by itself is seen in several non-diabetic conditions, an associated hyperglycemia is characteristic of diabetes mellitus. The urine volume is also increased (polyuria) in diabetes mellitus, as the term diabetes itself means. Thirst of a pronounced degree (polydipsia) and great hunger (polyphagia) are some of the other symptoms.

Diabetes mellitus is a condition resulting from an inability of the body to deal with glucose. In other words, there is an intolerance to glucose. This is the biochemical basis of this condition. The glucose tolerance test (GTT) is a very useful investigation in confirming the diagnosis of diabetes mellitus.

The subject is made to fast for 12 hours prior to the morning of the test, 50 gms of glucose (upto a maximum of 75 gms, depending on the weight of the subject) dissolved in a sufficient quantity of water and if necessary, suitably flavoured is given

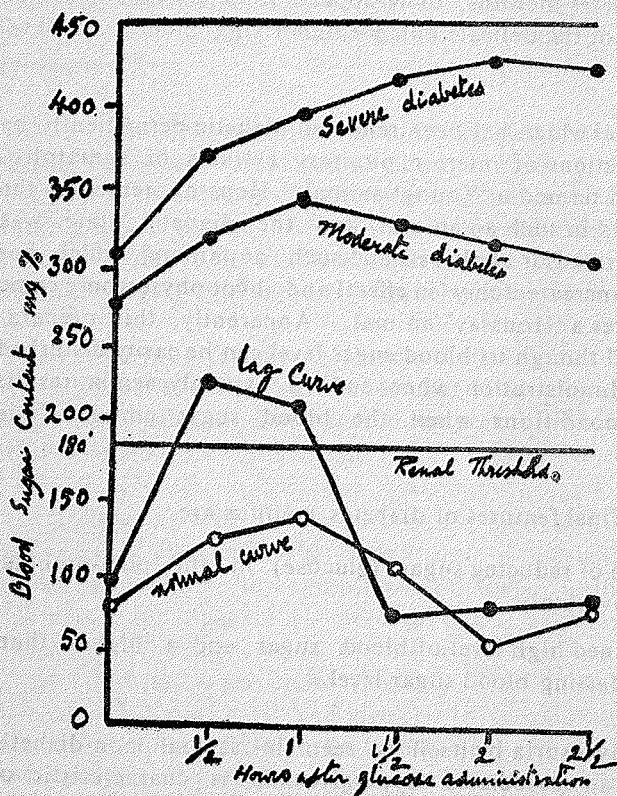


Fig 33. Glucose Tolerance Curves

orally after obtaining a sample of fasting blood from a vein, for determining glucose level. The bladder is also emptied at the same time and the urine is tested for the presence of reducing substances (glucose). Every half an hour, for about 3 hours, a sample of blood is taken along with a sample of urine. The samples are analysed. A graph is plotted showing the alterations of blood sugar content (Y-axis) with the passage of time—X axis (fig. 33).

In the case of a normal subject, the blood sugar level in the fasting state lies between 80 and 120 mg %. It rises to the maximum value in about half an hour to 1 hour after the ingestion of glucose. The peak value is, however, below the 'renal threshold' of 180 mg %. After this, it shows a decline to reach the original (fasting) level, within 2—2½ hours after administration of glucose. There may be even a fall below the fasting level (rebound effect) which lasts for a very short period before normal level is reestablished. The purpose of this procedure is to see if, when the body is suddenly loaded with glucose, it can deal with it sufficiently rapidly and dispose off the excess of glucose. The main mechanism by which the body is able to accomplish this is by putting forth an augmented secretion of insulin in response to the glucose load. The hormone sets into operation, processes which bring about assimilation and utilisation of the glucose administered. If the body cannot respond to the glucose stimulus by secreting insulin in adequate amounts, the condition is one of intolerance to glucose and diabetes mellitus is one such. The rebound effect (see a few lines above) is due to the continued action of the insulin secreted. The maximum to which blood sugar level rises is very much restricted in normal individuals who are habitually on a high carbohydrate intake. These subjects have a very brisk and efficient pancreas which can, on demand, secrete enough insulin to cope up with a large dose of glucose. Reducing substances (glucose) are absent in the urine in all the specimens.

In typical diabetes mellitus subjects, the fasting glucose level is itself high (above 120 mg %), the peak in the graph is above the so-called renal threshold value of 180 mg %. In severe diabetes, values as high as 300 mg or more may be seen. The

decline of the blood sugar level takes place rather very slowly, the fasting level being reached beyond the $2\frac{1}{2}$ hour period (from the start), unlike in the normal subject. The urine samples obtained after glucose intake may all show reducing substances in it. The fasting level and the highest value of the blood sugar concentration will depend on the severity of the condition. More severe the diabetes, higher will be the values and also longer the duration for the restoration of the fasting level.

In one class of subjects, the rise is very rapid, the peak value being higher than the renal threshold but the return to normal is as rapid as in a normal subject. Such a curve is termed a lag curve. The defect in these subjects is that the insulin response is not rapid enough though the total output of insulin is more than adequate. In view of the delay in the onset of insulin secretion, the rising phase and the peak values will make the curve resemble that of diabetes. These people are to be considered only as normal and not as diabetics.

Alimentary glycosuria: After injection of sugar, there is a high blood sugar level for a short time. This is due to fast absorption of glucose. This leads to glycosuria if renal threshold is exceeded. This condition is called alimentary glycosuria.

Renal glycosuria: In some people, the renal threshold for sugar is lower than in normals and so glycosuria occurs even when the blood sugar level is less than 180 mgm %. This is called renal glycosuria. In diabetics, it is said that the renal threshold may even be raised above the normal value.

Drug induced glycosuria: Phloridzin prevents the reabsorption of sugar in the renal tubules by inhibiting the enzyme phosphorylase. Phloridzin glycosuria is also called phloridzin diabetes. Alloxan, by destroying the beta cells of the islets in the pancreas, can cause a diabetes like state.

GLUCAGON

Kimball and Murlin, in 1923, indicated that there should be a separate hyperglycaemic factor produced by the islets of Langerhans of the pancreas. The name glucagon was given to

the new principle by them and it was found to be produced by the alpha cells of the islets. It is a polypeptide of 29 amino acids in its molecular structure and in the place of cystine, proline and isoleucine, as in insulin, it has methionine and tryptophane.

The provocation for the release of glucagon is a fall in the blood glucose level. The hormone, by its glycogenolytic action in the liver, attempts to restore the blood sugar level. It has no effect on muscle glycogen, unlike adrenaline. It may be of importance in a starving animal as it may act to maintain blood sugar level and ward off its fall. Glucagon is also known as the hyperglycaemic glycogenolytic factor (HGF).

Glucagon may even have mineralocorticoid-like action as regards the electrolytes, sodium, potassium and chloride. Glucagon seems to have a depressant action on gastrointestinal motility and it may reduce hunger contractions. Other actions attributed to glucagon are 1) in lipid metabolism—mobilisation of depot fats and releasing them into blood (hyperlipaemia), 2) breakdown of proteins.

Long acting insulins: The action of soluble insulin given by subcutaneous injection is quick in onset and lasts only for a few hours. This necessitates the giving of several injections in a day, resulting in discomfort and inconvenience to the diabetic patient. To avoid the disadvantage of using soluble insulin, other compounds of insulin like Globin Zinc insulin, Protamine Zinc insulin have been evolved. Their effect comes on with a greater time lag and lasts for a much longer duration than in the case of simple or soluble insulin. Soluble insulin is mixed with a compound insulin to combine the advantages of rapid and short lived action of the former with the delayed and sustained action of the latter. Thus, only one injection every day will suffice to keep blood sugar low. Certain oral preparations are used in the place of insulin in the treatment of diabetes. One of these is tolbutamide (Rastinon) which may provoke insulin secretion from the pancreas in mild diabetes. It is of no use in juvenile diabetes or in severe diabetes, in which condition insulin secretion is always totally absent.

MAINTENANCE OF BLOOD SUGAR LEVEL

The normal sugar content of whole blood (fasting sugar) is conventionally given as lying between 80 and 120 mg 100cc of blood. This value includes not only glucose, but so called blood sugar (60-90mg), but also glutathione, vitamin C and others which are not sugars.

There is a prime necessity to maintain the blood sugar level constant. The nervous tissue depends for its energy needs exclusively on blood glucose. If all the glycogen in the liver is converted to glucose without being replenished it will suffice to cater to the tissue needs only for a few hours. Muscle glycogen is not available for any other tissues. If blood glucose content suffers a diminution below 50 mg %, adverse symptoms follow, leading on to even death if remedial measures are not instituted immediately (see under Insulin). It is in this respect that the maintenance of blood sugar assumes paramount importance in the homeostatic mechanisms of the body. The blood sugar is remarkably constant in a wide variety of physiological states and even in starvation and on a high carbohydrate diet.

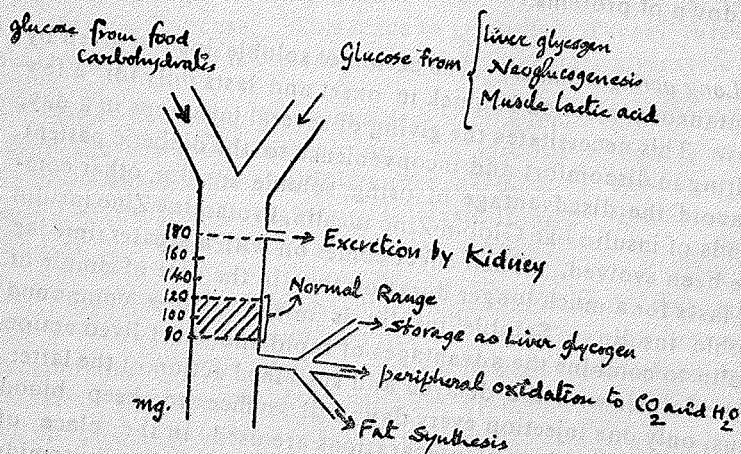


Fig. 34 (See text)

The mechanisms involved in the blood sugar level maintenance are of two kinds, each opposing the other in actions. One set of factors is directed towards adding on sugar to that already in the blood. The other is concerned with the withdrawal of sugar from blood as well as preventing further addition. These forces can be represented schematically with reference to a cistern or a reservoir which represents the blood vascular bed with inlets and outlets.

The mechanisms at play are as follows :

A) Ways in which blood sugar level can be elevated.

- 1) Food starch is digested and absorbed into the blood as glucose
- 2) Disaccharides, during digestion, are converted to monosaccharides and glucose is also derived from some disaccharides. Other monosaccharides are also converted to glucose.
- 3) Liver glycogen is broken down rapidly to glucose by the action of adrenaline and by glucagon and is discharged into blood.
- 4) Neoglucogenesis or conversion of non-carbohydrate substances like amino acids and glycerol to glucose are brought about mainly by glucocorticoids and also by the growth hormone.

B) Mechanisms concerned with bringing down the blood glucose level :

- 1) Utilisation of glucose by the various cells in the body, the glucose being withdrawn from the blood.
- 2) Conversion of blood glucose to liver glycogen.
- 3) Conversion of blood glucose to fatty acids and consequently promotion of fat synthesis.

Most of the hormones, with the possible exception of sex steroids and parathyroid hormone, are involved in blood sugar regulation and their actions seem to be located mainly in the liver which is, so to say, the central organ of blood

sugar maintenance. The liver appears to be set to a particular blood glucose level which it has to maintain with the aid of the various hormones. The glucocorticoids, to a major extent and the pituitary growth hormone along with thyroxine to a much less extent, are concerned with raising the blood sugar level by promoting neoglucogenesis. The glucocorticoids and the growth hormone seem to also inhibit peripheral utilisation of glucose by depressing the action of the enzyme hexokinase. Of the so called hyperglycaemic hormones (tending to raise the blood sugar), thyroxine promotes tissue oxidation of glucose to some extent, antagonising its own neoglucogenetic action. Glucocorticoids, while promoting neoglucogenesis, the predominant effect, strangely enough promote deposition of liver glycogen. In spite of the apparent contradictory action of glucocorticoids and thyroxine, these two, because of their overall action in elevating blood sugar, are hyperglycaemic in effect and along with the growth hormone, glucagon and adrenaline, are responsible for raising blood sugar level.

Of the hormones named above, adrenaline may be called the emergency hyperglycaemic hormone, since it is secreted as a quick response to a sudden fall in blood sugar level due to any cause. Its action in counteracting the fall in glucose level is by bringing about a rapid glycogenolysis in the liver, the glucose so formed being released into the blood stream. Glucagon seems to have a similar action, but whether it can also be considered as an emergency hormone, is not clear in the present state of knowledge.

In the early phase of prolonged starvation, adrenaline may be released to bring about a breakdown of glycogen in order to replenish the blood sugar that is rapidly being used up by the tissues. Adrenaline is effective only when hypoglycaemia is of sudden onset and of brief duration. Thus, there is a need to provide a sustained protection against a persistent hypoglycaemic tendency, as occurs in starvation of long duration. It is in this regard that the glucocorticoids, the growth hormone and thyroxine are important. These hormones, even after liver glycogen stores are depleted, help to prevent the fall in sugar level by mobilising protein and

fats in the body for the conversion into glucose (neoglucogenesis). Even ordinarily it is the action of these hormones by way of neoglucogenesis that prevent the blood glucose level from falling, in between the meals. To sum up, the actions of adrenaline and glucagon on the one hand and those of the glucocorticoids, growth hormone and thyroxine on the other hand, are mutually reinforcing and complementary.

While there is a formidable array of hormones, all meant for the prevention of a lowering of blood sugar content, yet there is only one hormonal agent bringing about a fall in the blood sugar level. Insulin is the sole hypoglycaemic hormone. Its actions and the mode of control of secretion have already been referred to. It must be stressed that when the blood sugar level rises above 120 mg or so, insulin secretion is induced as a feed back mechanism and the sugar level is brought down.

The autonomic nerves, vagus and sympathetic, can be taken to have an active role in the maintenance of glucose concentration of blood. When blood glucose level falls below normal fasting range there is a reflex stimulation of the sympathetic nerves, especially the splanchnic, which innervate the adrenal medulla. Secretion of adrenaline ensues and brings about a rapid return of the blood sugar to the normal range. The sympathetics do not play a direct role in the activation of adrenal cortex or of the adenohypophysis or even thyroid. Adrenaline acting through the hypothalamus and the adenohypophysis causes the release of ACTH and thyrotrophin and finally glucocorticoids and thyroxine respectively.

The pancreatic islets receive rich innervation from the vagus, stimulation of which results in insulin secretion. Apparently, the more effective way of stimulating insulin secretion is by means of a fall in blood sugar. Thus, there are two mechanisms regulating insulin release. It is believed that the feed back mechanism operating through a rise in blood sugar, is a crude form of control of insulin release. The vagus, perhaps provides a finer modulation of insulin secretion.

According to hitherto venerated ideas, when blood sugar content exceeds a certain level (renal threshold—180 mg%), glucose is excreted in the urine. So, when there is a marked hyperglycaemia, there is glycosuria also. The renal elimination of glucose, though a very crude mechanism, may also help in keeping down the blood sugar level, though glycosuria may not have such an obvious purpose.

LOCAL HORMONES

A number of these agents are released only in certain strictly restricted sites. They are not released into the blood stream in sufficient amounts to bring about generalised or systemic effects. They are, to mention the known ones—acetyl choline, histamine, heparin, 5—hydroxytryptamine, P—substance (pain producing substance in ischemic muscles), angiotensin and bradykinin. A few salient facts about each are mentioned in various appropriate places in the text. Bradykinin is a product of enzymatic action (snake venom, trypsin) on plasma globulins. This is usually a smooth muscle excitant though it acts as a vasodilator substance and brings about a fall in blood pressure. Pain nerve endings may also be stimulated by this chemical factor.

THE PINEAL BODY AND THE THYMUS

There are two organs with unproved and uncertain endocrine roles, the pineal body (epiphysis cerebri) and the thymus.

The pineal body is situated under the hind end of the corpus collosum and between the two superior colliculi. Embryologically, it arises as a diverticulum from the roof of the III ventricle, the cavity disappearing during development. This gland, if it can be so called, has an alveolar arrangement of cells and is also highly vascular. After about the 7th year of age, laminated bodies (brain sand) composed of carbonates and phosphates of calcium and magnesium appear in the substance of the gland. It was once fancifully known as the seat of the soul and also more 'definitely' as the

third eye. It has been found rather difficult to assign any proved physiological function to this structure.

Clinically, it has been observed that destructive lesions or tumours of this gland brought on precocious puberty in children, while growths of the gland tissue suppressed sex functions. Experimental lesions in animals have not produced any significant effects. The pineal tissue contains serotonin in appreciable amounts along with an enzyme to convert it to melatonin (so called because of its action on the melanocytes of the frog's skin) whose production follows a 24 hour (circadian) rhythm, the output of melatonin being more at night than in day time. One view is that the pineal body acts as a transducer or converter of nerve impulses (in retina) induced by environmental light, into chemical messengers—tryptophane derivatives—which being blood borne may have an endocrinal role in inhibiting gonadal activity. Darkness in the environment promotes the release of the hormonal agents, while light suppresses it. It is possible that this mechanism may have a role, even independent or complementary to that of the hypothalamohypophyseal action, in gonadotrophin release. As referred to elsewhere, in certain animals like the ferret and the pigeon, light plays a role in starting sex cycles or inducing ovulation respectively.

The thymus is found behind the sternum in the upper part of the thorax and since, on each side it develops from the third pharyngeal pouch, it should be considered as two organs - right and left. The peripheral part (cortex) of this gland contains lymphocytes in large numbers. The inner portion or medulla has less number of lymphocytes. Reticular cells of reticulo-endothelial system and spherical bodies formed by concentrically arranged spindle-shaped cells and going by the name Hassall's corpuscles, are other cellular elements of the medulla. The thymus has been considered to be associated with immunity reactions in a somewhat obscure way. At puberty, the thymus is found to have maximum weight and later in adulthood, it dwindles in size. After birth, lymphocytes appear to migrate to other parts of the body to start lymphocyte production in their new locations. Thymectomy in animals soon after birth, makes them highly susceptible to infections on account of failure of immunity reactions.

But the same operation in adult animal has no deleterious effects. Stress of any kind, inclusive of infection, causes regression of the gland just like the effect of cortisol administration. But when the stress is of a very sudden onset, an atrophy of thymus may not occur and death may ensue. In such subjects, the gland is found to be large at autopsy. These deaths were formerly considered to be due to a clinical entity - the status thymolymphaticus. Some doubt has been thrown on the implication that a large thymus is the cause of death. Most often, death occurred in young subjects in whom thymus was large in size. The atrophic small gland is found only in adults.

The disease, myaesthesia gravis, has also been considered to be a thymic disorder, but on insufficient grounds. This condition has been referred to in some more detail in the section on Muscle.

REPRODUCTION

Gonads: Testis and ovaries are the primary sex organs forming spermatozoa or ova respectively, and also secreting hormones which decide the apparent maleness or femaleness of an animal. The sex of an animal is ordained even when the ovum and spermatozoon unite and male or female sex is assigned to the embryo depending on whether the y or X chromosome is present in the sperm. Twentythree pairs of chromosomes are seen in a human cell. In the male, the members of one pair are dissimilar, with a small y chromosome and a large X chromosome.

Frecks in the determination of sex of the foetus: These result from probably chromosomal abnormalities or non-dysjunction of sex chromosomes. A few clinical syndromes or symptom complexes have been recognised as due to aberrations in sex development.

- a) Klinefelter's syndrome - The affected individual is genetically a female (with positive sex chromatin - see below) and possesses not only testes, though of small size, but also external characteristics of the female. His chromosomal configuration in the 23rd pair is XXy with a total complement of 47 chromosomes, instead of 46 or 23 pairs as in a normal subject.
- b) Turner's syndrome - This individual has only 45 chromosomes and only the X chromosome in the 23rd pair. He is negative with respect to the sex chromatin.
- c) Very rarely, a person may have 3 X chromosomes (XXX) in the 23rd pair (47 chromosomes in all) and is therefore known as a 'super female', though less feminine in appearance than a normal female.

Hermaphroditism: It is a word formed by the combination of Hermes the name of the Greek Messenger God and Aphrodite, the Greek Goddess of love. Sometimes, both testis and ovaries or even one testis and one ovary may be found in the same subject. The external genitalia may present a wide variety of mixtures of

the male and female types. The sex chromatin may be present or absent.

Pseudohermaphroditism: This is of two types—male and female—depending on what gonad is actually present, testis or ovary. It is in the development of the external genitalia that there is a mix up of both sexes. More commonly, the individual is a genetical female (+sex chromatin) with ovaries but with heterosexual development of accessory sex organs. The adrenal cortex may be responsible for this condition.

Sex Chromatin: It contains DNA and is Feulgen positive. The nucleolus itself has RNA and is Feulgen negative. It is seen as a small dot of chromatin near the nucleolus (nucleolar satellite) or near nuclear membrane, in the cells of females (Barr and Bertram body). Its presence in the male cells is rare. It is very useful in assigning the genetic sex in hermaphrodites. The cells of Malpighian layers of the skin show sex chromatin which is formed very early in life. This is of genetic origin and is believed to be derived from the heterochromatic portions of sex chromosomes, XX, which, when placed in juxtaposition, will produce the sex chromatin at the point of their contact.

Free Martin: In certain cases of twins of opposite sexes, the male is normal, while the female shows intersexual characters and is called the free martin. This is due to a direct communication between the circulations of the male and female embryos which occurs due to fusion of chorions. The male hormone is elaborated at an earlier stage in the male twin, which, when it reaches the female embryo, causes its masculinisation. Experimental injections of testosterone cause masculinisation of female guinea pig foetus. Similarly, opposite changes can be caused in male foetuses.

THE TESTIS

The testis (of which there are two) is the male gonad or primary sex organ. It has embryologically the same origin as the ovary (see ovary). At the time of puberty, it develops rapidly and consequently enlarges in size. The male secondary

sex characters appear concurrently and maleness of the individual is manifested. Secondary sex characters, male or female, are the visible signs that indicate the sex of the adult animal or human being. These, as mentioned already, appear at the time of puberty in either sex. The secondary sex characters of the male are as follows :

The birds :

- 1) In the omnivorous or insectivorous species, male is larger, while among the birds of prey the male is the smaller.
- 2) Special plumage or arrangement and development of feathers in the male, eg.— peacock. The peahen has a dull and drab appearance.
- 3) Certain appurtenances or appendages in the head of the male, as in the cock — comb, wattles and barbles. The legs of the cock have spurs attached to them.

Animals (mammals) :

- 1) Larger size due to greater muscular development in the male—the tiger and the lion provide the best examples.
- 2) The mane and the side whiskers distinguish respectively, the lion and the tiger from their female counterparts. The antlers of the stag or male deer, the beard of the goat, the larger teeth of the boar, are other characteristics of the male of the species.

In animals and birds of all species, there are prominent differences in the mental or psychological make up, between the male and the female. The male is noted for his aggressiveness, towards the female. The male pursues and courts the female prior to the mating act and setting up of a nest or starting a brood or litter.

Some of the sex differences between man and woman are listed below :

MAN	WOMAN
1. Larger stature (skeletal size) and greater muscular development and greater physical capacity and endurance.	Less height, lighter in weight and with poorer musculature.
2. Breast – rudimentary	Well developed and pendulous breast, especially in those who have borne children.
3. The skeletal differences are several and reference may be made to text books of Anatomy.	
4. Less of depot fat; skin rough and hairy.	Subcutaneous fat in thick layer giving a smooth contour to a woman's body. Smooth supple skin with great vascularity – women bleed more after injuries.
5. Facial (moustache and beard) and body hair in profusion. Scalp hair may become sparse (baldness), especially after puberty. Even otherwise, hair in the temporal regions of the scalp may be lost gradually.	Facial and body hair almost absent or very sparse and fine upto menopause (see under ovary) Scalp hair in plenty, usually.
6. Outline of pubic hair distribution – lozenge shaped and extends downwards from the umbilicus, the boundaries diverging away from it.	The outline is triangular with a horizontal top and tapering towards the perinium.

MAN

WOMAN

- | | | |
|----|---|--|
| 7. | Low pitched voice due to enlargement of larynx at puberty (breaking of voice) | High toned voice. |
| 8. | a) Higher basal metabolic rate.
b) Higher erythrocyte count
c) Smaller adrenals, thyroid and pituitary. | a) Lower BMR
b) Lower count
c) Larger glands, especially in women who have born children. |
| 9. | Psychological attributes – drive and aggressiveness; penchant for abstract thinking and to pursue objectives and ideals. Also more concerned with welfare of fellow beings. | Submissiveness to men, down to earth and practical approach to problems, devotion to family, self centred. |

There are accessory or secondary sex organs like the penis, the prostate and the bulbo-urethral glands are also to be considered as secondary sex organs in the male.

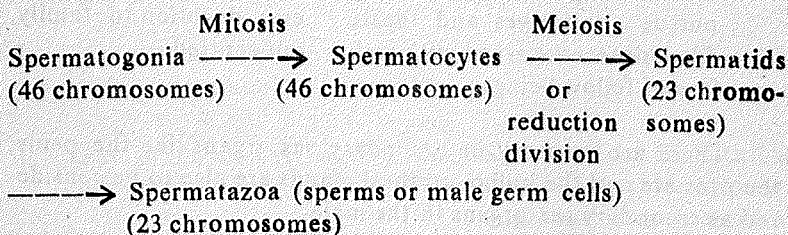
The Testis: The two testes are enclosed in the bag-like scrotum which retracts when environmental temperature is low on account of the contraction of the dartos muscle. The elephant and the sloth among land mammals are unique in that they have no scrotum, the testis being intra-abdominal. Rarely, even in humans, the testis, during its descent towards the scrotum, in embryonic life, may stop short and remain within the abdomen (undescended testis). Human chorionic gonadotrophin has been used therapeutically to promote the downward movement of the testis to finally come to rest in the scrotum.

The testis somewhat resembles a flattened egg invested by three coverings—the tunica vaginalis, the tunica albuginea and the tunica vasculosa from without inwards. It has two functional components – the seminiferous tubules concerned with spermatogenesis (formation of sperms) and the interstitial cells of Leydig which are seen in the spaces outside the seminiferous

tubules and these cells are responsible for elaborating the male sex hormones (androgens).

The testis is divided into 200-300 wedge-shaped lobules, each separated from its fellows by septa and containing 2 or 3 or more seminiferous tubules, each of which may communicate with others or commences with a blind end near the free border of the testis.

The seminiferous tubules are coiled tubes and are lined by a basement membrane on the inner aspect of which are spermatogonia. These cells divide to give rise to spermatocytes. The spermatids of smaller size arise from the spermatocytes and in their turn give rise to spermatazoa. Certain details of spermatogenesis are given schematically.



Spermatogenesis which commences at the time of puberty, continues for several decades upto an advanced age. Unlike in animals, there is no breeding or rutting season in the human male. Millions, and millions of spermatazoa are formed every day and as such the potential capacity of the male for procreation is astronomical (See under Ovary for comparison with women's capacity). Even when sperms are shed in large numbers daily by ejaculation, spermatogenesis is adequate to replace the lost ones. Strangely enough, sexual continence or restraint may somewhat depress spermatogenesis which is also depressed in illness. It may be permanently stopped by exposure to X-rays and other lethal radiations.

The spermatazoa (spermatazoon - singular) as they are formed, fill the seminiferous tubules and are attached to the cells of Sertoli (found lining the tubules) which are considered to have a nutritive function with regard to the sperms. The newly formed

sperms are non-motile and just by increase in numbers push the ones formed earlier, towards the epididymus which is a very highly convoluted tube. Motility and maturity are acquired by these cells while they are stored in the epididymus which may secrete some principle (spermatotrophic hormone) under stimulation by testosterone. Castration makes the sperms non-motile. If sperms are not expelled from the epididymus by means of seminal ejaculation, they degenerate and are absorbed. The sperms need a fluid medium for being suspended in and that is provided by the seminal vesicles, the prostate and the bulbo-urethral glands. The thick viscid fluid that results out of the mixing of sperms with the secretions of these glands goes by the name, semen. The seminal vesicle, a tubular gland, secretes a thick yellow viscous and alkaline fluid (containing fructose) which forms the major portion of the semen. The prostate is a gland with numerous follicles, ducts and muscle tissue and is responsible for an opalescent watery secretion which imparts its peculiar odour to the semen. Acid phosphatase (increased in blood in cases of prostatic cancer), fibrinolysins, calcium and citrate are some of the constituents of the secretion of this gland. (for more particulars regarding semen, vide Fertilisation).

The Endocrine Function of the Testis: It was Berthold's work in the last century that revealed the influence of the testis in the male sex functions. He removed the testes in a male bird, the domestic cock. Certain visible changes occurred. The bird lost its masculine attributes like the comb, the wattle and the spur, all of which atrophied. It also lost its male aggressiveness. On grafting back the gland, these structures developed again.

Castration (removal of both testes) is a very ancient practice. Human captives were castrated, to be employed as palace guards by kings of old. The bull was castrated for increasing its stature and enabling it to perform more work. Horses have also been castrated. In the human male, castration in childhood (traumatic now a days) will result in the following changes.

1. Pubertal changes – development of secondary sex characters and secondary sex organs (see above) does not take place. Skeletal growth may or may not be accelerated.

2. The voice remains high pitched, since the larynx does not enlarge.
3. The normal sex instinct does not develop and hence there is no libido.
4. Spermatogenesis and production of androgens will not commence.
5. Skin will be smooth. Scalp hair will be plentiful and baldness does not set in. The body contour will be that of a woman.

In the adult male, castration may bring about atrophy of the secondary sex organs and impotence results. But libido persists. Voice changes do not occur. Facial hair is not lost.

The now common contraceptive operation of tying the vas deferens or even severing it does not produce any adverse effects at all and is not to be considered as similar to castration. Spermatogenesis and anrogen production go on. In some cases, ecranalisation or reunion of the vas has been performed leading on to a favourable result.

Non-descent of the testis from the abdomen into the scrotum (cryptorchidism) seems to interfere with spermatogenesis but if the interstitial cells are normal, hormone secretion will continue and the subject for all appearances will look a male with all the attributes. Surgical correction (orchidopexy) is resorted to in appropriate cases – the testis is brought down and embedded in the medial aspect of the thigh. Hormonal treatment may also be tried. It is a moot point whether, in cryptorchidism, the the higher temperature in the abdomen (than in the scrotum) is inimical to spermatogenesis. It is no hindrance in the case of the elephant with abdominal testis. High environmental temperature in the tropics does not affect spermatogenesis even though the scrotum and hence the contained testes, are liable to be warmed. In compensation, the pampiniform plexus of veins in the testis may provide a cooling device for the testis in order for spermatogenesis to go on without interference.

Androgens: These hormones are so called because, on administration, they promote the precocious development of secondary sex organs and secondary sex characteristics in imma-

ture male animals and boys and after castration in young boys and young male animals and birds. It prevents regression or atrophy of secondary sex organs in castrated male adults including birds and animals. Androgens are also concerned with increasing and maintaining the motility of sperms stored in the epididymus. In hypophysectomised animals, spermatogenesis is maintained by large doses of androgens. Though, Butenandt in 1931, isolated androsterone, the first androgen to be prepared in a pure state, later, when testosterone was obtained from testicular tissue, it was identified as the true testicular hormone and androsterone was found to be a degradation product of testosterone which was about 5-10 times as potent as androsterone. The molecular configuration of these two steroids is given in Fig. 35.

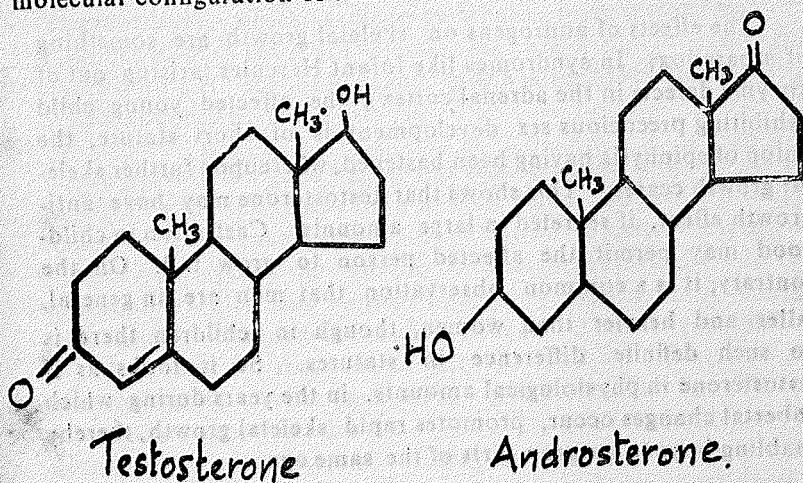


Fig. 35 Male Sex hormones

These substances may be derived from cholesterol through pregnenolone. Testosterone is inactivated in the liver if it is orally administered. It can be given as sublingual tablets of methyl testosterone which is absorbed into blood through the buccal mucous membrane. Androgens are converted to a 17-ketosteroid (dehydroepiandrosterone) and this is excreted in the urine. It is this contribution from the androgens that raises the 17-ketosteroid output in the male urine above that in the female whose urinary 17-ketosteroid is derived entirely from adrenocortical hormones.

The anabolic effects of androgens: While it may be considered as a growth hormone in that it brings about the development of secondary sex organs, in addition it promotes retention of nitrogen (protein deposition in muscles) resulting in a positive nitrogen balance, in a manner similar to the pituitary growth hormone. This action is known as the anabolic effect and based on it, it has been used clinically to bring about increase in body weight in young boys with testicular insufficiency and also in elderly subjects when emaciation and loss of weight may need to be corrected. Special types of androgens which have only or mainly anabolic effect and lack androgenic properties, have been evolved for therapeutic use.

The effects of androgens on skeletal growth are something of a paradox. In syndromes like Infant Hercules (arising out of enzyme defects in the adrenal cortex), the affected young child exhibiting precocious sex development is of short stature, the union of epiphysis having been hastened, whereupon further skeletal growth ceases. This shows that testosterone may have anti-growth effect, if secreted in large amounts. Castration in childhood may permit the affected person to grow tall. On the contrary, it is a common observation that men are in general, taller and heavier than women, though in children there is no such definite difference in statures. So it looks as if testosterone in physiological amounts, in the years during which pubertal changes occur, promotes rapid skeletal growth, thereby enabling boys to outgrow girls of the same age.

Testosterone has an undesirable action in that it may promote prostatic cancer, symptoms of which (pain mainly) are at least ameliorated by female hormones. Castration also has beneficial effects in this condition.

Regulation of the Testis' functions: The adenohypophysis secretes two gonadotrophic hormones – the follicle stimulating hormone and the luteinising hormone, both of which exert control over the male gonad as follows:

Extirpation of the pituitary in pre-pubertal animals prevents the development (at the age of puberty) of secondary sex organs and the appearance of secondary sex characteristics, on account

of the absence of testicular hormone. In adult animals, testis atrophies. In pituitary deficiency states also, poor or arrested development of testis has been noticed.

When an extract of the anterior pituitary lobe or the Luteinising hormone is given to animals that have undergone removal of pituitary, testosterone secretion ensues and in turn, spermatogenesis is reestablished. The luteinising hormone is called the interstitial cell stimulating hormone (ICSH) in the male, since it promotes the secretion of testosterone. FSH promotes spermatogenesis by a direct action on the seminiferous tubules. Since it has a similar action in the female towards the maturation of the Graafian follicle, FSH has been referred to as the gametokinetic hormone, which seems to be a better term than FSH, since it applies to both sexes. The action of FSH is potentiated in the presence of LH. In the absence of the latter, the former has a less pronounced action.

In the decades gone by, it was wondered whether the usual negative feed back between a target gland and the pituitary, operated in the case of the testis. Castration causes certain histological changes in the hypophysis, like increase in the number of basophils which take on the 'signet ring' appearance. Androgen administration prevents such a change. The testis, by means of its hormone (or some other factor), inhibits the release of gonadotrophins. After castration, gonadotrophin titre (level) in blood is higher than before. The feed back mechanism, as revealed by certain observations, may not be due to testosterone. When there is a primary testicular failure, injections of testosterone do not diminish the gonadotrophin output, whereas oestrogen is effective. The testicular inhibitory factor may even be some agent other than testosterone.

THE OVARY

At the time of conception, if the sperm uniting with the ovum has an X-chromosome, the resulting embryo will be a female one.

The ovary is the female sex organ (gonad). There are two ovaries, one on either side in the abdomen near the fimbriated end of the fallopian tube.

Structure and the development of ovary: The ovary and the testis arise from coelomic epithelium over the inner aspect of Wolffian body. The epithelial cells assume columnar shape and proliferate to form several layers constituting the germinal epithelium. The underlying mesoblast thickens, forming genital ridges. Fingers of mesoblast grow upward into germinal epithelium and columns of germinal epithelium grow down resulting in interlocking. The genital epithelial cords break up into cell nests from which the Graafian follicles and convoluted seminiferous tubules develop. A layer of germinal epithelium covers the ovary. It is cuboidal in childhood and flattened in adult women. The mesoblastic tissue around cell nests gives rise to the stroma of ovary as also vascular tissue. The adult ovary has the shape and size of a shelled almond, with a stroma of connective tissue with blood vessels, containing a number of follicles embedded in it and these are seen to be in different stages of development. A few smooth muscle fibres are present in the stroma. The germinal epithelium of the ovary is continuous with peritoneum. Groups of epithelial-like cells are seen in the ovarian stroma of many animals and these are called interstitial cells. These are absent in the human ovary but some scattered cells alike in appearance may be seen and they may serve a purpose like that of the interstitial cells.

Graafian Follicle: The germinal epithelium retains its embryonic character and potentialities from birth till menopause. One cell of the cell nest becomes the ovum with the surrounding cells forming a covering, the granulosa cells. This primordial follicle is without a cavity and is 0.5 mm in diameter. It migrates from the surface deep into stroma. The ovum itself governs the development and arrangement of granulosa cells. (Cords or clumps are formed irregularly in the absence of ovum when the ovum is destroyed by X-rays). In immature girls 400,000 primordial follicles are present. At puberty, the follicle acquires two more layers of stroma.

- 1) the inner layer – theca interna. It is vascular and cellular and is influenced by granulosa cells. Theca interna cells are large and polyhedral in shape with oval nuclei.

- 2) Theca externa—fibrous in nature and cells fusiform in shape. As these layers are formed, granulosa cells multiply and form two more layers which are each several cells deep with a cavity (the antrum) between them, lying on one side of the ovum and liquor folliculi collecting in it. The cells in immediate contact with the ovum forms a heaped up mass called cumulus oophorus or discus proligerus. Enlargement of the follicle occurs, accompanied by increasing collection of fluid, as ripening of the follicle progresses. The follicle now moves towards the surface of the ovary and projects from the surface. When fully developed, rupture of the follicle occurs with ovum being discharged into the peritoneal cavity. The ovum is about 70μ in diameter with a clear, deeply stained cell membrane, the zona pellucida. The ovum enters the fallopian tube and moves along it to reach the the uterine cavity. Ripening of follicles with discharge of ova does not occur till puberty. Regular crops of 20 or more of primordial follicles appear during every menstrual cycle. Only a few develop fully and discharge ova — one or occasionally two and very rarely more, in every cycle. The other follicles are necessary for hormone production. The pain of ovulation caused in some people is known as Mittelschmerz. Only about 400 ova are discharged in the sex life of a woman (15th to 45th year of age, approx.). The remaining follicles undergo atrophy or attrition and are replaced finally by fibrous tissue from theca interna. A small scar, corpus fibrosum, remains. The rupture of the follicle is probably due to distension caused by fluid. Smooth muscle of stroma may play a part in this. The follicle ruptures in the rabbit, the cat and the ferret only after copulation.

Functions of ovary: 1) Gametogenesis or production of germ cells. 2) Endocrinal activity 3) Formation of corpus luteum. 4) control of menstrual changes in uterus during menstrual cycle. 5) Preparation of the uterus for pregnancy. 6) Control of development of mammary gland to make milk secretion possible after pregnancy.

The activity of the ovary is modified as follows: 1) ovulation provoked by copulation in cat and rabbit; visual stimulation in

pigeon, or experimental stimulation of hypothalamus or whole brain in rat and rabbit.

- 2) Excessive light provokes sexual activity during hibernation in certain animals.
- 3) Cold inhibits ovarian activity and sexual cycle.
- 4) Infections suppress menstrual cycle. Undernourishment has same effect.
- 5) Thyroid insufficiency or removal, retards sex development. Moderate hyperthyroidism increases frequency of cycle, but a severe condition of this type suppresses the cycle.
- 6) Adrenal hypo and hyper functions disturb ovarian function. Optimum level of thyroxine and adrenal hormones are necessary for normal ovarian function.

Female sexual life : Sex life starts at puberty, when the first ovulation occurs. Accessory sex organs develop and sexual desire is aroused. During this sexual period, mating or sexual or breeding seasons occur recurrently. The ovary secretes 2 times more oestrogen in adulthood, than in childhood. Mating season is twice in a year for a bitch, and is of six weeks duration. In man, no particular mating season exists, though fertility is greatest from April to June. During mating season, cyclical changes occur in the genital organs. If one cycle extends throughout the mating season (as in a dog), the animal is called mono-oestrus. If several occur in a mating season, the animal is polyoestrus, as in cat, mice, cow, sow & rat.

Oestrus cycle in mono-oestrus animal : 4 phases —

- 1) Prooestrus — Coming on of heat period. Swelling and congestion of external genitalia with growth and increase in vascularity of uterus, are the prominent features. Engorgement of mammary gland takes place and bleeding from vagina also occurs. The Graafian follicle undergoes maturation, prior to ovulation.
- 2) Oestrus — (phase of intense desire) Heat means prooestrus along with Oestrus. Female receives the male and ovulation occurs.

- 3) **Pseudopregnancy** – Uterine changes progress with marked proliferation and secretory activity of uterine glands. The mucosa thickens and blood supply increases. These changes depend on corpus luteum. The growth of mammary gland is stimulated. All uterine changes are in anticipation of the arrival of fertilised ovum. When this fails to occur, uterine fabric breaks down, the debris is discharged and repair ensues. But if pregnancy occurs, changes progress and merge with pregnancy. The corpus luteum has a very short life in polyoestrus animals like rat and mouse. Luteal activity is prolonged and more intense in animals exhibiting pseudo-pregnancy.

- 4) **Anoestrus**: It is the quiescent period between mating seasons. In some animals, there is no phase of pseudo-pregnancy and oestrus is followed by metoestrus.

In polyoestrus animals, the quiet period between oestrus cycles is called dioestrus. Anoestrus is a long period of rest between mating seasons.

Cytological changes: Prooestrus is signified by large nucleated epithelial cells. Oestrus – The presence of squamous cornified cells with stratification into layers and filled with mucus, is a diagnostic feature. During dioestrus or anoestrus, large number of leucocytes are present along with a few epithelial cells and mucus.

Ovarian hormones: 1) **Oestrogens**— follicular hormone or female sex hormone—oestradiol, oestrone and oestriol.

- 2) **Progesterone** or corpus luteum hormone. Oestrogen is concerned with prooestrus and estrus and progesterone with pseudopregnancy and pregnancy.
- 3) **Relaxin**.

Oestrogen: Evidence from ovariectomy and grafting experiments prove its role. Allen and Doisy extracted it from liquor folliculi of hog's ovaries. Cells of origin of the hormone are not definitely known. Probably, theca interna cells secrete oestrogen and are the chief source of it. But even if follicles be destroyed, hormone is still produced. Interstitial cells also secrete it. Oestrogen is found in many animal tissues — blood,

muscle and urine of pregnant and non-pregnant females, in urine of males and even in testes. Strangely enough, the richest source of oestrogen in nature is the stallion's (male horse) urine. A high concentration of oestrogen is seen in the urine of women after 2nd or 3rd month of pregnancy. The human placenta also is a source, especially in later months of pregnancy. It is also found in the corpus luteum and in foetal membranes, amniotic fluid and in adrenal cortex.

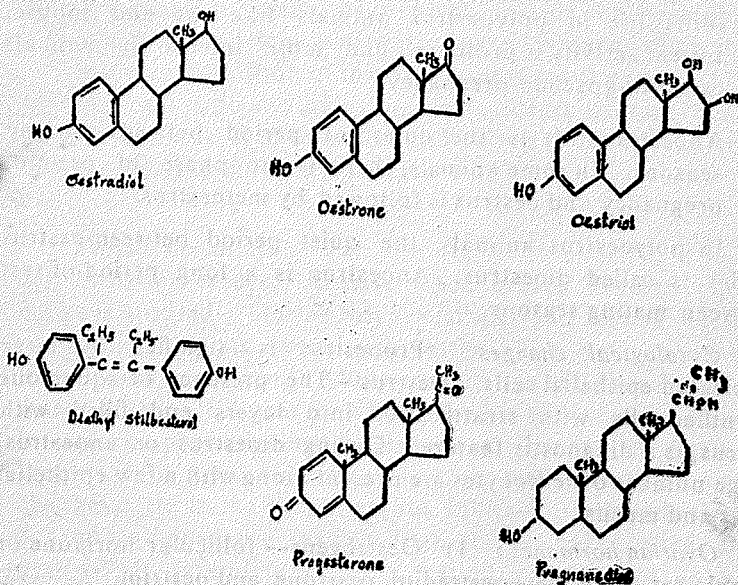


Fig. 36 Female Sex hormones

Oestradiol or dihydroxy oestrin—a form may be the true oestrogenic hormone. It is 10 times as powerful as oestrone and 50 times as oestriol. This may be converted to oestrone and oestriol in the body.

Oestriol is excreted in pregnancy urine as glucuronate and is inert as such. But just before labour, free oestriol is excreted. The uterus is protected from the excessive action of oestrogen by detoxication in the liver. The synthetic nonsteroid compound Diethyl-stilboestrol is effective orally with 2 or 3 times the potency of oestrone. But only 60% activity is seen when taken

orally. Two allied compounds Dinoesterol, and Hexoesterol are also available. A cause and effect relationship seems to exist between oestrogenic substances and carcinogenesis. The cell proliferation caused by the action of oestrogen in the uterus is similar to early stages of malignancy. Ovariectomy reduces the incidence of cancer in susceptible strains of mice. Ovarian tumours are associated with hypertrophied endometrium. Conversely, certain carcinogenic substances have oestrogenic activity.

Actions of oestrogen: 1) Induces oestrus in immature or ovariectomised mice. Even psychic changes occur in conformity with oestrus. Cuboidal epithelium in vagina of childhood is converted to more resistant squamous type.

Cytological changes: Oestrogens provoke increase in thickness of vaginal epithelium and cornification of superficial cells, Oestrogenic activity results in preponderance of superficial chorio-picnotic and cornified acidophil cells.

- 2) Prevents atrophy of accessory sex organs, after spaying (removal of ovaries).
- 3) Is responsible for development of secondary sex characters. Typical hair growth in females is due to oestrogen. Pubic hair triangular with flat upper margin (In men, pubic hair boundary is lozenge-shaped). Skin becomes smooth and soft. Androgens make skin thick and tough. In the female, skin is more vascular and so more warm and women bleed more from injuries.
- 4) Though it accelerates growth at puberty, yet a limit is imposed on skeletal growth, causing union of epiphysis with shaft. Female eunuch grows taller than normal girls. Pelvic growth may be due to an effect on bones. In males, oestrogen acts synergistically with androgens, to develop male secondary characters. Excess oestrogens in male may cause breast development. In young males, some feminisation may be brought about.
- 5) Prevents nidation of ovum and induces abortion in early pregnancy.
- 6) Causes hypertrophy of adrenal cortex through the release of ACTH.

- 7) Promotes growth of uterus in pregnancy through local action of placental oestrogen.
- 8) Is responsible for the development of the duct system in breast.
- 9) When repeatedly injected, causes atrophy of ovary and testes, due to suppression of pituitary gonadotrophins.
- 10) In spayed monkeys, after administration is stopped, menstruation may occur.
- 11) Exhibits synergism with oxytocin towards the end of pregnancy, when free oestrogen appears.
- 12) Acts as a primer for progesterone action and is necessary for maintenance of corpus luteum.
- 13) Water retention is caused with increased blood volume and extracellular fluid volume — mineralocorticoid activity.
NaCl retention and diminished Ca and P excretion in urine.
- 14) Ameliorates symptoms of prostatic cancer growth.
- 15) In menopausal stage, granulosa cells cause rejuvenation and reappearance of menstrual cycles. Thecomas also have similar effects and rarely may cause masculinisation changes.

Oestrogen action on growth : Causes increased osteoblastic activity. So, at puberty in female, growth rate is rapid for a few years. Subsequently, skeletal growth ceases, due to union of epiphysis with shafts of long bones. So, growth in female stops several years earlier than in the male. Female eunuch grows much taller than a mature female, because epiphyses do not unite. The broadening of the pelvis may be a byproduct of oestrogen action on skeletal growth. Oestrogens also cause retention of phosphate and calcium. Elevation of plasma Ca occurs reason for which is not known. Increased fat deposition occurs in characteristic places. Oestrogens in large quantities potentiate effects of growth hormone and cortical hormones in raising blood glucose level and in causing diabetogenic effect. Oestrogens and testosterone have opposite effects on breast, sexual glands, prostate and sex characters. Their antagonism is mediated through the anterior pituitary by suppressing G. S. H. release.

To antagonise oestrogen effect on breast, 50 times more of testosterone must be given.

PROGESTERONE

This is secreted by the luteal cells of corpus luteum. When ovulation occurs, the follicle is filled with a blood clot which is later replaced by cells containing yellow lipid material. These cells are derived from proliferation of granulosa and theca interna cells. Capillaries penetrate into the yellow cell mass, which functions as a gland. Corpus luteum persists for 10 days after ovulation and then regresses. Vessels get occluded, cells disintegrate and a pale scar, corpus albicans, remains.

During pregnancy, corpus luteum grows upto $\frac{3}{4}$ " till middle of pregnancy, then regresses and disappears after the 7th month. To sum up, corpus luteum persists in pregnancy, during lactation, pseudo-pregnancy in animals and after hysterectomy in some animals.

Pregnanediol is an inert reduction derivative of progesterone, excreted as a conjugate of glycuronic acid. Pregnanediol glucuronate appears in urine, a day or two after ovulation, becomes maximum a week before menstruation and disappears 2 or 3 days before menstruation. It is excreted in urine throughout pregnancy, in large quantities — maximum between 8th and 9th months. Liver detoxicates progesterone.

Corpus luteum is essential for pregnancy. Abortion occurs, if it is removed, because of lack of progesterone. It is not indispensable after 4th or 5th month, as placenta takes over the secretion of progesterone.

Actions: a) 1. Causes changes of pseudopregnancy and premenstrual changes in uterus.

- b) 1. Promotes implantation of ovum and influences development of placenta (growth of decidual tissue of uterus)
2. Brings about the development of alveolar system of mammary gland.
- 3) Causes suppression of oestrus and also ovulation.

- 4) Reduces susceptibility of uterus to oxytocin but make immature rabbit uterus more sensitive to adrenaline. Normally, non-gravid uterus of rat, cat and mouse is inhibited by adrenaline, but progesterone causes adrenaline to excite the uterus in these species.
- 5) Softens and relaxes pelvic ligaments and thereby leads on to extensibility of symphysis pubis.
- 6) Suppresses uterine motility during pregnancy.
- 7) a. Prolongs pregnancy and prevents abortion after spaying or hypophysectomy, and even in some normal animals.
b. Prevents superfoetation by suppressing GSH secretion of anterior pituitary.

Functions of Corpus luteum are same as above.

Experimental evidence for actions of progesterone (hence of corpus luteum): 1) There is no corpus luteum in mammal without placenta – marsupials and monotremes – kangaroo and other Australian animals.

- 2) Destruction of corpus luteum results in abortion.
- 3) Prolongation of pregnancy occurred, if pregnancy urine was injected into animals. Larger and more mature foetuses resulted.
- 4) Loeb reaction – Irritation of uterine mucosa (in non-pregnant animal), by a thread or glass bead, caused a deciduoma to develop. This occurs only if corpus luteum is intact or if progesterone is injected.
- 5) Pseudo pregnancy changes occurred after ovulation which itself resulted from 'sterile' copulation.
- 6) Mammary gland growth can be correlated with corpus luteum development.
- 7) The corpus luteum inhibits follicular maturation. Squeezing of corpus luteum of cow through rectum hastened next cycle. Suppression of ovulation by progesterone prevents superfoetation.
- 8) Injection of corpus luteum extracts caused progestational changes (pseudo pregnancy) in uterine mucosa of castrated adult rabbits, when the uterus was primed by oestrogen. Oestrogen must always be given before progesterone, to make the latter effective.

Oestrogen initiates progestational changes and corpus luteum stimulates secretory activity and causes final alterations in mucosa to receive the ovum. Oestrogen is also necessary for the development of the corpus luteum of pregnancy and for the continued action of progesterone on uterine mucosa, as well as for the softening and relaxation of the ligaments by progesterone.

RELAXIN

It can be prepared from luteal tissue, free of progesterone and oestrogen. It is a polypeptide. It causes relaxation of the ligaments of symphysis pubis in the guinea-pig. Even oestrogen or progesterone, separately or combined, cause similar effects. But after hysterectomy, such effects are not seen. So it is concluded that oestrogen and progesterone release relaxin from uterus. Also relaxin acts more promptly than oestrogen or progesterone and relaxin is effective even after hysterectomy.

GONADOTROPHINS (G. S. H.) OF ANTERIOR PITUITARY

Atrophy of gonads occurs in diseases of the anterior pituitary gland and after hypophysectomy. Crude saline anterior pituitary extract (effect of growth hormone, combined with those of follicle stimulating hormone—F. S. H. and luteinising hormone—L. H.) caused enlargement of graafian follicle with luteal cells packed in it and the ova imprisoned in it. Grafting of anterior pituitary caused the enlargement of ovaries. Super-ovulation was also brought about. Vaginal epithelium was altered from columnar to squamous type. Ovulation and oestrus occurred in mature animals. The development of the gonads and accessory sex organs took place in immature animals. FSH causes liberation of oestrogen by stimulation of the Graafian follicles. Pregnancy urine contains gonadotrophins. Prolan A and B are old terms for FSH and LH respectively.

Actions — FSH: 1) Causes ripening of Graafian follicle, super-ovulation, production of small corpus luteum.

- 2) Oestrogen production is stimulated and oestrus is also caused.
- 3) Increases formation of sperms in testes due to epithelial proliferation.

L. H.: 1) Brings about extensive luteinisation with retained ova.

- 2) Stimulates the secretion of progesterone.
- 3) Inhibits oestrogen release and suppresses changes of oestrus phase.
- 4) Interstitial cells are stimulated in testes and hence it is called the interstitial cell stimulating hormone (ICSH) in the male. Testosterone secretion is promoted.

LH potentiates FSH action in causing proliferation of theca and granulosa cells so that more oestrogen can be secreted. LH is said to be responsible for ovulation though FSH may also be involved. Ovulation occurs when LH secretion is maximum.

FSH and LH act synergistically like oestrogen and progesterone. FSH primes ovaries for LH action. After hypophysectomy, LH will not act on uterus unless primed by FSH or oestrogen.

Some workers were of the view that both FSH and LH were one and the same substance but that the action depended on the dosage and also the stage of the sexual cycle. This notion has been given up now. They are chemically different and pure preparations with distinctive actions have been obtained. Still some doubt exists. FSH is also called gametokinetic hormone.

Maintenance of the corpus luteum does not depend upon LH only. The initial action of LH is maintained by luteotrophin or prolactin (modern view).

Pituitary exerts some control over ovulation for, hypophysectomy within one hour of copulation, in rabbit, prevents ovulation. There may be no specific ovulation principle but only that ovulation may result due to a proper balance between the levels of FSH and LH.

Afferent impulses from genital tract call into play the pituitary response leading on to ovulation. But copulation may not be necessary as even sexual excitement itself may be enough. Pituitary influence on ovulation is of central origin and is dependent on nervous integrity. Ovulation may occur due to stimulation of cervical sympathetic, hypothalamus and the hypothalamico-hypophyseal fibres or may even be caused by convulsant drugs. Ovulation

is of nervous origin in lower animals. Thus, many influences may call for a pituitary response. This is abolished however, by cutting the pituitary stalk or by section of the lumbo-sacral cord which blocks proprioceptive impulses from hind limbs. So, though genital sensations may elicit pituitary response, they are not essential. Even sexual excitement with associated postures for copulation, appears to be sufficient. Even adrenaline liberated due to excitement, excites the pituitary (direct application of adrenaline to pituitary is effective).

FSH initiates sexual activity — psychic changes of puberty appear and oestrus or menstrual cycle starts. Changes in accessory organs and stimulation of gonads are brought about with onset of sex cycles. LH acts specifically on granulosa and theca cells to produce progesterone.

Gonadotrophins probably are produced by basophils of anterior pituitary. After castration (in rats), basophils increase in anterior pituitary with increase of GSH content. Castration cells (basophils) appear — large vacuole in cell pushing nucleus to one side — signet ring appearance. If a castrated male is united parabiotically to a female hypophysectomised rat, super-ovulation with a large number of follicles is seen in the ovaries. Ovaries exert a restraining influence on GSH release of anterior pituitary. Continuous oestrogen administration causes atrophy of ovary through suppression of GSH. Anterior pituitary itself shows increase in chromophobe cells with decrease in basophil and acidophil cells. Probably, the two phases of ovarian cycle are controlled by the mutual interaction of ovarian and pituitary hormones. Pituitary gonadotrophins are not excreted normally in urine. But after ovariectomy, pituitary GSH may appear in urine. So also, after menopause. Rarely, it may appear in normal urine without any cause. This, unlike HCG (see below), is effective when tested on normal monkeys or hypophysectomised animals (difference between GSH and HCG).

THE MENSTRUAL OR THE ENDOMETRIAL CYCLE

In the primates only, the reproductive organs pass through a series of changes in a repetitive manner — the menstrual cycle of which bleeding from the vagina is the most evident feature.

Studies have been made by observing endometrium transplanted into the monkey's anterior chamber of eye. Oestrogens produced dilatation of the vessels of the graft, thus stressing the endocrine nature of the changes. In woman, changes are seen in the extra-uterine patches or growths of endometrium in the broad ligament, ovary, peritoneum, even vulva and perineum or laparotomy scars. The ectopic tissue bleeds during menstruation—(endometriosis – not very uncommon).

Rhythmical variations in the activity of anterior pituitary are primarily responsible for the regularity of menstrual cycle.

3 Phases: The menstrual cycle is, (Fig. 37) for descriptive purposes, considered as consisting of three phases, one after another. There is a hormonal basis for this division.

- 1) **Stage of repair and proliferation** (6–14 days after onset of previous menstruation). This is also known as the follicular phase (some divide this into 2 periods — regeneration phase and proliferative phase). It lasts for about 9 days, from the 6th day after previous menstrual bleeding. Uterus enlarges due to stromal growth. Blood vessels increase in number and length with coiling of arteries and hypertrophied endometrial glands also showing proliferation. Ovulation occurs at the end of this phase, which corresponds to pro-oestrus in lower animals. Oestrogen is responsible for uterine changes.
- 2) **Pre-menstrual or secretory phase — Luteal phase:** (15th – 28th day) Changes of the first phase become more marked. Uterine mucosa shows much hypertrophy and great vascularity. Even glands are elongated and take on the appearance of cork-screws. Increased secretion of glands, of mucoid nature occurs. This phase depends on corpus luteum action and also oestrogen which continues to be secreted (corresponds to pseudopregnancy of lower animals). Towards the end, uterine mucosa resembles the decidua of pregnancy. But blood vessels become constricted at the end of this phase. Mild psychic changes—mental depression and irritability—are characteristic features. Pre-menstrual tension—fluid retention - occurs and weight increase by 2 to

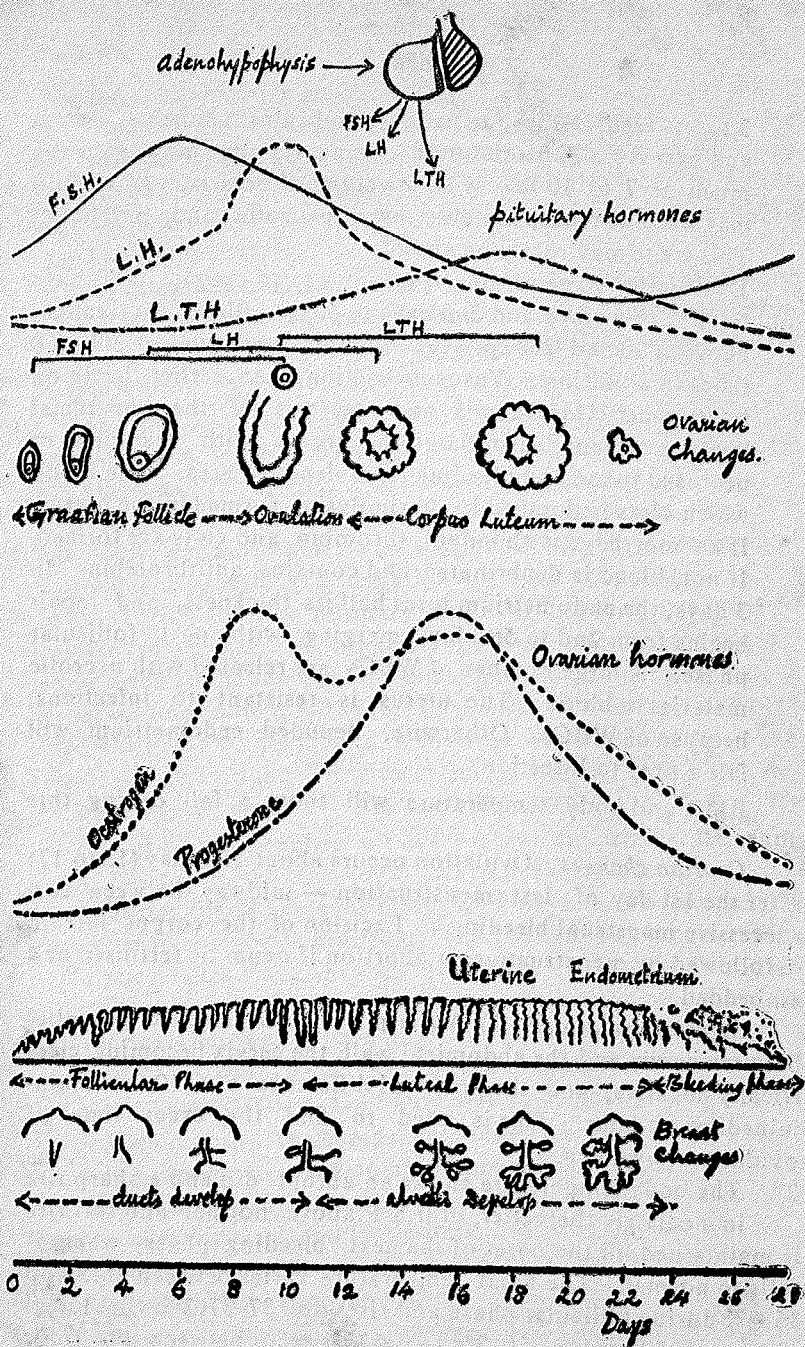


FIG. 37. THE MENSTRUAL CYCLE

3 lbs. is seen. Once menstruation begins, diuresis occurs and excess weight is reduced. Some women may gain as much as 7 to 10 lbs, with swelling of breasts. A woman may become tense, irritable, even neurotic and psychotic. This stage may rarely be absent.

- 3) Destructive stage of menstrual flow: (4 days). 3-7 days in 95% of women and 3-5 days in 60%. Blood loss ranges between 20 and 200 cc. A woman menstruates 300-500 times in a lifetime. Vasoconstriction seen earlier leads on to endometrial ischaemia and necrosis of the superficial layers. Then vasodilatation occurs with shedding of necrosed tissue and bleeding from denuded area. The blood which clots is liquified by fibrinolysins formed in the uterus. If haemorrhage is abundant, thrombin and clots are formed. If not, blood is defibrinated and contains antithrombin. In 3 days, the endometrium loses half its thickness, and repair begins from 2nd to 5th day, merging with next follicular phase. A large number of WBCs are released with necrotic material in blood. The uterus is resistant to infections, because of WBCs. Otherwise, denuded endometrium will fall a prey to infection.

BMR and body temperature will show a fall during this phase.

Ovarian changes: Ovulation occurs about 15th day (13 to 17) after the 1st day of last menstruation — midway between two successive menstrual bleedings. Excision of the corpus luteum is followed by menstruation or abortion if ovum is fertilised and embedded.

Signs of ovulation: 1) A sharp rise in the electric potential between cervix and the abdominal wall, the cervix becoming electrically negative, and the potential difference of 6-10 mv maintained for an hour. This is used to find the exact time of ovulation in women.

2) The body temperature shows an abrupt dip and a sharp rise immediately thereafter, of 0.8°F above normal and this rise is maintained till the onset of the next bleeding phase, when it falls to normal. The basal temperature varies between 36.3 and 36.8°C during follicular phase and rises to 37-37.3°C in luteal phase. A difference of 0.3°C to 0.5°C is seen between the follicular and luteal phases in ovulatory cycles.

- 3) Pregnanediol appears in urine a day or two after ovulation.
- 4) Increase of cornified acidophil cells occurs in vaginal smear, at the time of ovulation.
- 5) Increase in urinary gonadotrophins is also seen just before ovulation occurs.

Two maxima are seen in the blood levels of oestrogen — one at the time of ovulation and the other a week before menstruation — i. e. at the height of the development of corpus luteum. A sharp fall occurs before the onset of menstrual bleeding.

Oscillatory cycle theory: The rhythm of menstrual cycle once initiated, is perpetuated by interaction between the pituitary gland and the ovary. First, due to stimulation of the ovary by FSH, oestrogen level increases in the body fluids. But if it exceeds a certain value, the output of FSH is suppressed. Consequently, oestrogen secretion is now diminished. LH is released from anterior pituitary and this causes progesterone release from ovary. As progesterone level rises, LH release is suppressed so that corpus luteum regresses bringing down the progesterone content in blood and tissues. The level of oestrogen also has by now fallen, and menstrual bleeding occurs. As a result of this (due to low level of oestrogen), FSH secretion is once again resumed. The cycle is repeated.

In girls, as the pubescent ovary begins to secrete more and more oestrogen, the duration of ovarian cycles becomes shorter and shorter till an average period of 28 days is reached; and the production of both oestrogen and FSH becomes adequate. Ovulation takes place, making the woman fully sexually mature. Female sexual cycle appears to be principally due to reciprocal oscillation between production of FSH by pituitary and of oestrogen by ovary. This occurs even in the absence of enhanced progesterone secretion, as in anovulatory cycles.

Menotoxin: An atypical euglobulin is produced by endometrium similar to necrosin of inflammatory exudates. Menotoxin is found in menstrual blood and also in general circulation, and is said to cause vascular lesions. Menotoxin is said to be released due to involution of corpus luteum and decrease in oestrogen and progesterone.

Fertilisation of ovum: The ovum is fertilised by a single sperm which penetrates the zona pellucida to gain access into

the interior of the ovum. The cells of the cumulus oophorus disperse prior to the entry into the ovum of the sperm and this effect is made possible by the large number of sperms which provide sufficient hyaluronidase. Hyaluronidase inhibitors like trigentesic acid or rihibin, when added to rabbit semen, prevented fertilisation. So also, phosphorylated hesperidin. But this compound was even found to be anti-contraceptive. Hyaluronidase inhibitors did not affect fertility.

Factors concerned with causation of menstrual flow: In monkeys, bleeding occurs between mating seasons, without ovulation. Anovulatory menstruation occurs occasionally in women, especially the first few cycles in girls are so. The corpus luteum is not, however, formed in these cases. The progestational changes in the endometrium are not absolutely essential to the menstrual cycle. These seem to be only incidental. But the changes in the follicular phase, due to oestrogen, are absolutely essential.

Abrupt fall in oestrogen level in blood seems to be important for the onset of menstruation.

Evidence in favour: 1) Bilateral ovariectomy in women or monkeys, causes uterine bleeding, indicating the cause as the withdrawal of an ovarian hormone.

- 2) In an ovariectomised monkey, after some injections of oestrogen, its withdrawal is followed, in a few days, by bleeding which is prevented by giving oestrogen again. Progesterone administration following oestrogen withdrawal, will prevent bleeding.
- 3) Maximum oestrogen release occurs in the inter-menstrual period and little before the onset of menstruation.
- 4) A few days after an injection of GSH, bleeding occurs. Ovariectomy abolishes this bleeding.

The role of progesterone is not clear, though degeneration of corpus luteum and cessation of progesterone secretion coincides with or precedes menstrual flow.

Corner's hypothesis: Menstruation is caused by a sudden fall in progesterone secretion due to involution of corpus luteum. In anovulatory cycle, however, menstruation is due to withdrawal of oestrogen.

Puberty and Menopause : The very first menstruation, called menarche, occurs as early as 10th year in tropics. Period of sex awakening is called puberty. Menopause occurs between 45 and 50 years of age (average 47). Menstruation ceases and accessory organs atrophy. Other changes like narrowing of vagina, shrinkage of breasts, are all due to ovarian atrophy. Graafian follicles disappear and fibrosis occurs. Menopause can be induced by X-ray irradiation of ovary.

Female climacteric : It lasts from several months to several years, during which sexual cycles become irregular and gradually stop. A woman must adjust her sexual life, which was previously maintained by oestrogen production, to that without an endocrinal basis. Both Oestrogen and progesterone decrease rapidly after last menstruation. Symptoms due to loss of oestrogens :

- 1) Hot flushes (extreme vasodilatation of skin) and sweating.
- 2) Psychic features of irritability, fatigue and anxiety and even psychotic states occasionally. Sex libido may not alter much.

Oestrogen may be present in blood and urine years after the onset of menopause. GSH is increased in urine, and oestrogen diminished. 15% of women need treatment for menopausal symptoms, with diethyl stilbesterol in small doses at first and gradual diminution of the dose. But such treatment prolongs the symptoms. During menopause, a tendency to obesity and virilisation — hair growth on upper lip and body occurs (attributed to androgenic cortico-adrenal hyperfunction).

Post-pubertal castration causes changes similar to menopause, but more abruptly. But this differs from sex infantilism because secondary sex organs and characters are already developed. Hair growth in body after castration in women, is perhaps due to loss of inhibition of oestrogen on hair growth.

Menstrual irregularities :

Metrorrhagia — Intermenstrual bleeding.

Metrophathia Haemorrhagica : Continuous bleeding. Endometrium is thickened, with dilated glands and areas of necrosis. A constant finding is an unruptured cystic follicle. Excess of FSH production and prevention of corpus luteum formation may be responsible for endometrial changes.

Epimenorrhoea : Prolonged bleeding, with intermenstrual period shortened. Menstrual disorders are seen also in hypo and hyper-pituitarism.

Amenorrhoea : Absence of menstruation as occurs in hypothyroidism, anaemia, tuberculosis and malnutrition. Primary amenorrhoea is not amenable to treatment, though oestrogen and progesterone together may give results. It is needless to say that amenorrhoea results from pregnancy and lasts for the duration of pregnancy. In secondary amenorrhoea, hormonal treatment is helpful and efficacious. Progesterone is used in excessive bleeding.

Hypomenorrhoea : Scanty menstrual flow.

Hypermenorrhagia : abundant flow.

Oligomenorrhoea : Menstruation at long intervals. Opposite of Polymenorrhoea.

Dysmenorrhoea is painful menstruation, due to spasmodic uterine contractions.

Therapeutic uses of sex hormones :

- 1) Oestrogens are used to increase menstrual flow if scanty. Testosterone and progesterone or HCG alone or together with oestrogen and testosterone are used for excessive bleeding.
- 2) Oestrogens are very useful in menopausal syndrome.
- 3) Oestrogen is used for treatment of gonorrheal vulvo-vaginitis, in children. Columnar epithelium becomes cornified and stratified, as in adults, and hence will be resistant to infection. Oestrogens are also used in pruritis vulvae.
- 4) Progesterone is used in sterility or habitual abortion. It is also useful in dysmenorrhoea. In metrorrhagia, progesterone combined with oestrogen, gives good results.

NASO-GENITAL RELATIONSHIP

Mucosa over intra-nasal conchae, has erectile tissue like penis and clitoris. Nasal congestion and epistaxis (bleeding from the nose) may occur regularly in some women, coincident with the bleeding phase of menstrual cycle and at puberty in both sexes. Sometimes, menstrual bleeding may be absent, but epistaxis may alone occur (vicarious menstruation — wrongly called so).

FERILISATION, PREGNANCY, FOETAL PHYSIOLOGY AND PARTURITION :

Fertilisation : This means union between spermatozoon and ovum. The term conception also refers to the same event.

Erection : The penis lengthens and hardens, and becomes rigid and erect. Blood accumulates in erectile tissues of the penis – two corpora cavernosae and one corpus cavernosum erythrae, which expand into the glans. If the erect penis is tied at the base (in an animal), it remains erect till ligature is removed. Distension is due to dilatation of afferent arteries, and not produced by ligating the veins. Stimulation of 1st, 2nd or 3rd sacral rami, causes profuse bleeding if corpora cavernosae are cut, in the dog. Flow diminishes when stimulation is stopped. Also, cessation of stimulation of nervous erigens brings on increased venous flow (10–15 times), and erection is abolished. B. P. falls in the arteries and rises in the veins during erection and this is brought about by activation of parasympathetic fibres and provoked by cutaneous stimuli, especially those applied to genital regions and particularly on the mucosa of the glans. Friction during the sex act, first causes erection and then ejaculation. Other stimuli are associated with sexual excitation. Even the very thought of the sex act can provoke erection. Emotional stress and psychic inhibitions may, on the other hand, inhibit erection.

Pathway of erection reflex :

Afferent : Dorsal nerve of penis, a branch of internal pudendal nerve. Section of the nerve prevents sexual excitement in animals.

Efferent : Nervous erigens, whose peripheral course is in the internal pudendal nerve itself.

Castration abolishes erection even though nervous erigens is stimulated. In man, fibres from 2nd to 4th sacral nerves conduct impulses centrally. Sectioning of thoracic sympathetic fibres produces disturbances in erection.

Ejaculation : The production of sperms in testes is continuous. They are moved along the genital tract by cilia of epithelial lining of epididymus and vas deferens and by their own motility. They get deposited in the ampulla of vas. The seminal vesicles are not reservoirs for sperms. Cowper's glands and epithelia of

genital ducts contribute fluid which forms a substantial part of the ejaculate. The contraction of the vas during ejaculation, empties the sperms through ejaculatory ducts into the urethral opening on each side of the veru montanum. The seminal vesicles, Cowper's glands and the prostate pour out secretions into the urethra. The veru montanum becomes turgid and the internal urethral sphincter contracts, preventing entry of sperms into the bladder. The seminal fluid collects in the membranous part of urethra, having been pushed into it under pressure by the contraction of the vas, seminal vesicle and the prostate. The external sphincter suddenly relaxes, the bulbo cavernosus and ischiocavernosus and levator ani contract and relax rhythmically, reciprocally with the contraction and relaxation of the sphincter. Thus, semen is ejected. Ejaculation is reflex in nature. Ejaculatory centre is situated in 4th and 5th lumbar segments in the rabbit, slightly higher than the centre for erection. Afferent impulses arise in the glans and urethral mucosa. Efferent fibres arise from upper lumbar segments and from adrenergic lumbar sympathetic fibres. These fibres cause contraction of vas and seminal vesicles. Other fibres – from 3rd and 4th sacral segments travel in internal pudendal nerve to ischiocavernosus and bulbo cavernosus and sphincter urethrae. If parasympathetic sacral fibres are cut, ejaculation is abolished. Also, if sympathetic lumbar fibres are cut, emission of sperms does not occur and sperms may go into the urinary bladder. Removal of lumbar sympathetic fibres below 12th dorsal segment produces disturbances in ejaculation. Emission of seminal fluid can occur without erection. In rodents, asphyxia can cause ejaculation. Ejaculation is accompanied by pleasurable sensations and motor phenomena which all constitute the orgasm which is followed by muscular relaxation, flaccidity of the penis and a sense of fatigue.

Seminal fluid: Volume ranges between 2 and 5 cc. (average 3.2 cc) with 40×10^6 to 300×10^6 sperms in 1 cc. (average 90 million / cc). The quantity is diminished with increased frequency of copulation. Normal forms of spermatazoa are from 60 to 100% of the total (average – 82% in fertile man). Motility – 40 to 90% (average – 61%). Minimal requirements for fertility are 2 cc of semen with 20 million sperms per cc. 40% actively motile (3 of Hotchkiss–Macleod scale). Normal forms upto 60% of the total.

Motility is related to fertility. Chemically, the fluid contains large amounts of fructose (200 – 800 mgm/100cc), choline, phospho-choline, citric acid and acid phosphatase. Fructose and choline are from seminal vesicles. Acid phosphatase and citric acid are from prostate. Androgens stimulate their production and castration diminishes the concentration of these substances. Semen clots on standing, and in lower animals plugs the vagina, so that the cervix is stimulated and corpus luteum involution is retarded. Clear serum separates after clotting. The clotting enzyme is called vesiculase.

The seminal vesicles add fluid to the sperms, but their extirpation does not prevent copulation, though fertility is diminished. The prostate adds its own secretion to the semen. The prostate enlarges by about the 40th year of age in nearly 50% of men. Periurethral glands also enlarge. The enlarged prostate may obstruct evacuation of urine. The prostate is supposed to have endocrine functions necessary for reproduction and to maintain the vitality of the sperms, though no actual principle is definitely identified. Removal of the prostate does not interfere with copulatory capacity (potentia caecunde) or cause changes in sex characteristics. But fertility may be diminished due to mechanical obstruction to emission, after prostatectomy. Prostatic development is influenced by androgens. Pre-pubertal castration causes prostatic atrophy. Same result is seen even in old people after castration. Androgenic treatment increases growth, if given before puberty. Oestrogens inhibit development. Castration and oestrogens alleviate pain and prolong life, in prostatic cancer. Even adrenalectomy is done for the same purpose. In prostatic cancer, blood acid phosphatase increases. Stimulation of hypogastric nerves causes contraction of smooth muscle fibres in prostate. Pelvic nerve stimulation has same effect, but emission is not promoted. Sympathetic cholinergic fibres seem to innervate prostatic glands, just like sweat glands. Testosterone diminishes and oestrogen increases the excitability and contractility of the vas deferens, seminal vesicle and the prostate.

How the released ovum (from ovary) enters the fallopian tube, is not known. Even if one ovary is removed and the opposite fallopian tube is tied, ova enter the remaining fallopian tube. Th ciliated epithelium of the uterine tubes promote a flow of

fluid towards the uterus. Peritoneal fluid is continuously moved into the fallopian tube. Thus probably, ova are enabled to move into the fallopian tube.

Fertilisation occurs most often in the lateral $1/3$ rd of the fallopian tube. Rarely, it may take place near the ovary itself, or in the uterine end of the fallopian tube. The released ovum has a mass of granulosa cells – the corona radiata. The sperms travel up the genital tract at a rate of 4 mm / minute, thus taking 30 mts to reach the fimbriated ends of the fallopian tubes. Hyaluronidase of sperms disperses the corona radiata and one sperm reaches the ovum. It is possible that a large number of sperms is necessary to provide enough hyaluronidase. Once a sperm enters the ovum, the remaining sperms are inactivated. The head of the sperm swells up as soon as it enters the ovum, and the rest of the cytoplasm including the tail is dissolved. The swollen head of the sperm becomes the male pronucleus. Just then, the second polar body is given off from the ovum, so that its nucleus becomes the female pronucleus. At the same time, a centrosome, derived from the sperm, appears between the two pronuclei. This divides into two centrosomes which move to the opposite poles of the ovum. The two pronuclei fuse to form a new nucleus with a full complement of forty six chromosomes, and mitotic division commences soon after. Fertilisation and first cell division may take place within several hours to half a day after copulation. The fertilised ovum moves towards the uterus, arriving there within 2 or 3 days, due to ciliary action and peristaltic movement in the fallopian tube. But, as the fallopian tube has a rugged inner surface, full of pockets, the passage of the ovum is impeded so that cell division can occur before its entry into the uterus. While in the fallopian tube, a trophoblast is formed. This exhibits phagocytosis and may thereby utilise the secretions of fallopian tubes for nutritive purposes. Three to six days elapse in the uterus before implantation of the ovum takes place. Thus, 6-9 days is the time taken for implantation after fertilisation. At the time of arrival in the uterus, the embryo is in the blastocyst stage with trophoblast cells outside. The trophoblasts secrete digestive enzymes to burrow into the endometrium which is ready to receive it. Also, the blastocyst together with endo-

metrial cells will form the future placenta and foetal membranes. Nutrition of embryo, initially, is from glucose, proteins, fats and minerals stored in the decidua. The blastocyst cells absorb the nutriment from the decidua and deliver it to the embryo. This goes on for a few weeks at the most. Then placenta which by now is well formed, takes over.

THE PLACENTA

When the blastocyst cells invade endometrium, blood vessels and the mesenchyme grow into the trophoblastic tissue and at the same time blood sinuses with blood from mother develop in the endometrium between the blastocyst and decidua. The embryonic vessels grow into the blastocyst covered by the chorion. The foetal villus is covered by chorion and blastocyst. The capillaries in the villus are covered by thin endothelium, outside of which is a layer of mesenchyme and still outside of this is a thin layer of trophoblastic syncytium. So placental membrane is at least three cells thick and so is much thicker than the alveolar membrane in the lung and the capillary membrane elsewhere.

Foetal blood is separated from maternal blood through a double layer of epithelium, one of maternal and another of foetal origin. Later, these two fuse. Chorionic villi are lined by two layers—1) cells of Langhans and 2) a syncytium. The permeability of the placenta gradually increases from almost nothing at 8 weeks to a maximum between 32 and 36 weeks and diminishes towards parturition due to deterioration. But even at maximum permeability, it is much inferior to the ordinary capillary membrane. Large lipid molecules pass through it with difficulty. Also O_2 , glucose, CO_2 , Na^+ etc. pass through it less easily than through the capillary membrane or the partition between the alveolar air and the pulmonary capillary blood.

Thickness and vascularity of the placenta increase during pregnancy. At 15th day, it is 0.5 cms thick and at 60th day it is 0.7 cms thick. Stroma cells become decidual cells — large epithelial cells and these get shed after parturition and hence called decidua. When the embryo penetrates the endometrium, a mucosa lined chamber is formed. Mucosa, lining the uterus outside the embryo, is called decidua vera or parietal decidua. Mucosa, covering embryonic chamber

but separating it from the uterine cavity, is decidua reflexa. The embryo is separated from uterine wall which is lined by decidua basalis or serotina. The decidua vera is thick and vascular in the beginning of pregnancy, but from 4th month it thins out, and at full term it is only 1-2 mm thick. Decidua reflexa also diminishes in thickness and by 6th week only traces remain. In the 5th month, the decidua reflexa fuses with decidua vera completely. The decidua basalis forms part of the placenta (the maternal part), the chorionic villi forming the foetal part.

Functions of placenta: 1) Respiratory 2) Nutritive 3) Excretory 4) Storage 5) Endocrinal.

- 1) Respiratory: { Maternal blood saturation (oxygen)
 { Arterial — 95%
 { Venous — 69 %
 { Foetal blood saturation (oxygen)
 { umbilical artery — 15 to 45%
 { umbilical vein — 70 to 80%

In the maternal blood sinuses, there is at least 65 mm of Hg oxygen tension. In foetal villi, it is 50 mm of Hg. So 15 mm tension gradient is present. Circulation through maternal sinuses is slow enough to supply adequate oxygen, even though pressure gradient is 15 mm. Foetal haemoglobin attains only 90% saturation. In the last month, oxygen saturation may fall below 80% and just before labour, to 65%. Fall in saturation may be due to decreased permeability of placenta to oxygen.

Carbon dioxide: The difference in tensions of carbon dioxide, between maternal and foetal bloods is much smaller but, since carbon dioxide has a higher diffusion coefficient, it passes through, rapidly. Respiration, initially, is through the interstitial fluid before placenta is formed. During second half of pregnancy, foetus grows at a faster pace than the placenta. So oxygen saturation of foetal blood falls. In advanced pregnancy, maternal venous blood is only 20% saturated. Active oxygen secretion by placenta is assumed to occur, but this view is not accepted. The dissociation curve of foetal haemoglobin differs from that of adult haemoglobin in that foetal haemoglobin has greater affinity for oxygen than adult haemoglobin, especially at oxygen saturation below 70%. The foetus is always in a state of relative anoxia. During foetal life, a few rudimentary respiratory

movements are present. At birth, due to 1) asphyxia during labour and 2) reflexes provoked by cold tactile stimuli or painful stimuli, respiration commences. Anaesthesia to mother depresses the excitability of respiratory centre of the foetus. So foetal asphyxia will result. Slapping or immersing a child alternately in warm and cold water, usually stimulates respiration if it stops. A more efficient way is to inflate lungs rhythmically with a mixture of oxygen and carbon dioxide (5% and at less tension than 15 mm Hg). Lobeline is also injected into umbilical vein. Foetal atelectasis disappears completely only after deep inspiratory movements and complete expansion of lungs does not take place at birth, but occurs over a few days.

- 2) *Nutrition*: Glucose in foetal blood is 20–30% lower than in maternal blood. So it diffuses from maternal blood to foetal blood. Similarly, amino acids, Ca, phosphate, sodium and chloride pass through. Rapid utilisation by foetus helps in transfer, by maintaining a lower concentration in foetal blood. The trophoblast cells may even actively absorb nutrients from maternal blood in early pregnancy, or even throughout. Sometimes foetal blood contains more amino acids, Ca^{++} phosphate etc. But the concept of secretion is not widely accepted.
- 3) *Excretion*: Loss of carbon dioxide and urea is effected through the placenta. Creatinine diffuses out of the foetus less easily.
- 4) *Storage*: Placenta, in the first few months, grows much faster than foetus and stores proteins, calcium and iron.
- 5) *Endocrinal Function*:
The placenta secretes three hormones. These are –
1) HCG – Human chorionic gonadotrophin or anterior pituitary – like (APL) substance.
2) oestrogen and 3) progesterone.

HCG has both FSH and LH actions but more of the latter. HCG is said to be secreted by cytotrophoblast or Langan's layer. It is called APL substance because it is a single substance with pituitary hormone – like action (FSH and LH combined) but differs in many ways from any known pituitary principle.

Nature of HCG: Human placental extracts or those prepared from human pregnancy urine, caused maturation of Graafian

follicle, oestrus and ovulation with formation of corpus luteum, in immature rats. But LH type of action is more pronounced. Pituitary LH action is ineffective in immature animals because priming action of FSH is absent. HCG causes pituitary to release FSH, on the other hand, and so is effective in immature animals. HCG has less effect on ovaries (enlargement) than pituitary GSH. Similar action of HCG is seen on the testis. HCG has been used in the treatment of undescended testis. HCG maintains integrity of seminiferous tubules in hypophysectomised animals but, unlike pituitary principles, cannot prevent ovarian atrophy after hypophysectomy, for it requires the aid of FSH. In birds, however, HCG has no action on immature testis though ICSH is effective. HCG is absent in placenta of lower animals. It disappears in urine promptly after parturition. It is found in large amounts in urine in hydatidiform mole, chorion epithelioma and in teratoma.

Pituitary does not contain more GSH in pregnant state than in non-pregnant state. Animals which are resistant to HCG will respond to GSH and vice versa.

Actions of HCG and the urinary principle are identical, as the latter is derived from the former. HCG supplements pituitary in maintaining corpus luteum. So the placenta, by its hormone HCG acting through ovary, perpetuates its own activity.

PREGNANCY TESTS

Ascheim Zondek test: 2 cc of pregnancy urine are divided into six doses and given over a two-day period to immature female mice aged 3 to 4 weeks. Changes are seen in ovaries as described below:

- 1) Ripening of Graafian follicles and oestrus.
- 2) Haemorrhages occur into some unruptured follicles and blood spots about the size of a pin head are seen on the surface of the ovary.
- 3) Luteinisation of follicles with retained ova – these are called atretic corpora lutea.

Changes 2 and 3 appear within 100 hours and are fairly diagnostic (99% positive) even as early as 5th day after the 1st day of the missed period. Change (1) is not specific and occurs in other

conditions — after menopause and in carcinoma. It is positive in the chimpanzee and man. The test depends on presence of living chorionic placental tissue and production by it of HCG which acts synergistically with FSH of anterior pituitary. The test is positive in placental growths, hydatidiform mole and chorion epithelioma and tubal pregnancy. It is positive before abortion, but negative after abortion actually occurs. Metastatic chorion epithelioma also gives positive result. In man, teratoma gives positive results. Also pituitary tumours producing GSH excessively, answer this test.

Friedman's test: Adult rabbits are used and tests take shorter time — only 24 to 48 hours. Female rabbits are isolated, to avoid ovulation. 10 cc of pregnancy urine is given intravenously as a single dose. This test has the same value and significance as the A. Z. test.

The discovery that toads and frogs of both sexes could be utilised for pregnancy tests has led to widespread use of these easily obtained animals. The South African toad (female), *Xenopus*, was injected with pregnancy urine in the dorsal lymph sac (Hogben test). In a few hours (upto 12 hours), the animal laid eggs, accumulating to form a mound. Frogs also respond to HCG. The male frog produced sperms which could be detected microscopically in the cloacal fluid.

Recently, immunological tests have been devised. Rabbits have been induced to form antibodies to HCG and thereby the rabbit serum has been used for complement fixation, haemagglutination and precipitin tests. Sheep's red cells coated with HCG were found to clump when exposed to rabbit's anti-HCG serum, in about 2 hours from the start of the test. This cuts down the duration of the test drastically and it is expected that this test will replace the older animal tests which may become obsolete soon.

The urinary excretion of the HCG rises very steeply at about the end of the 4th week after the first day of the missed period, reaching a peak at about the 9th week and declining very rapidly initially and later gradually to fall to a low level at about the 20th week. A smaller rise is seen at about the 36th week and a fall to zero at the end of pregnancy.

After the 3rd or 4th month of pregnancy, HCG secretion decreases and corpus luteum begins to involute. Now placenta itself elaborates oestrogen and progesterone.

Oestrogen secretion increases towards the end of pregnancy to 25-30 times the maximum value in non-pregnant state. It causes proliferation of all tissues during pregnancy. Also, foetus may need it for its non-specific or general growth, especially of sex organs. Progesterone secretion increases 10 times towards the end of pregnancy. Progesterone inhibits uterine movements and causes the development of decidual tissue. Also, oestrogens along with progesterone, prepare the breasts for lactation.

Placental Progesterone: This is produced by the syncytial layer of placenta, though this is not proved. About a third of the total output in pregnancy is secreted by placenta. A little contribution comes from the adrenal cortex.

Evidence: 1) Excision of corpus luteum in later months does not cause abortion in lower animals and in women.

2) In rats (corpus luteum persists upto parturition), removal of ovaries and all foetuses but one, permits pregnancy to continue.

Corpus luteum does not secrete large quantities of progesterone until it is further stimulated by luteotrophin which causes corpus luteum to secrete both oestrogen and progesterone and it alone maintains the corpus luteum even without FSH and LH which are no longer necessary once luteotrophin begins to be secreted. Maximum oestrogen and progesterone secretion occurs at about the 22nd day following the onset of menstruation and decreases rapidly to a very low level on or about 26th day. Small quantities of oestrogen suppress FSH secretion and increase that of LH and luteotrophin.

After ovariectomy, secretion of LH and luteotrophin is markedly reduced and only FSH is secreted. So, oestrogen blocks FSH release and promotes LH and luteotrophin release. This is a specific effect of oestrogen. Progesterone has similar inhibitory effect on anterior pituitary hormonal release and especially on the release of LH and luteotrophin.

Other hormones in pregnancy:

The adrenal gland enlarges and secretes more of its hormones. Thyroid also enlarges and secretes more to meet combined foetal and maternal demands. The parathyroid enlarges so that adequ-

ate blood calcium level is maintained for foetal use even by withdrawing from maternal bones. Anterior pituitary increases in size, secreting more of TSH, ACTH and growth hormone. But GSH production is suppressed due to the negative feed back effect of oestrogen and progesterone secreted by placenta.

FOETAL PHYSIOLOGY

Foetal growth: Initially, placenta and foetal membranes grow more rapidly than foetus. (first 2-3 weeks). Later, foetus; grows in proportion to age—12 weeks—10 cms; 20 weeks—25 cms; 40 weeks—50 cms. The weight increases in proportion to cube of length. — 1 lb at $5\frac{1}{2}$ months; 3 lbs at 32 weeks; $4\frac{1}{2}$ lbs at 36 weeks and 7 lbs at birth. Male babies are heavier than female babies.

Blood: Blood cells appear at 4th week in yolk sac, and at 5th week in foetal mesenchyme (refer to section on blood). Liver and lymphoid tissues stop producing cells several months before full term. Initially, due to great development, there is relatively more blood. At birth, quantity of blood is $\frac{1}{10}$ th of the body weight. The placenta, at birth, holds 100 to 125 cc and will yield 75-100 cc to the child. The cardiac output of foetus is relatively more (several times) than in the adult because of (relatively) larger blood volume.

Foetal circulation: The lung and the liver are not fully functioning. The blood from the placenta (oxygenated) enters the body through the ductus venosus and after bypassing the liver to a large extent, enters the right auricle through the inferior vena cava and is shunted into the left auricle through the foramen ovale. Thence it enters the left ventricle to pass on to the aorta and to cerebral vessels. Venous blood from the head and upper limb enters the right auricle and then to right ventricle and pulmonary artery. From this vessel, the ductus arteriosus carries most of the blood directly to the aorta. The two streams in the right auricle, one from the inferior vena cava and the other from the superior vena cava, do not mix. The head and the upper limb get oxygenated blood. The lower limbs and abdomen are supplied with only partially oxygenated blood and that is why they do not grow in proportion to the size of the head which is larger relatively than the rest of the body, at birth. The liver

receives only $\frac{1}{3}$ rd of its blood supply from the portal vein. The venous blood from the liver is drained into the inferior vena cava through suprahepatic veins. Blood from the viscera and the lower part of the body is drained through the umbilical arteries into the placenta. The change from foetal circulation to post-natal circulation may be abrupt or spread over a few days after birth.

Changes at birth: When lungs expand, pulmonary arterial pressure falls. The closure of the umbilical arterial system causes aortic pressure to rise. So, blood attempts to flow back from the aorta to the pulmonary artery through the ductus arteriosus. Perhaps, due to the valve-like folds of endothelium in the ductus arteriosus, it closes in a few hours to a few days after birth. Because of the fall of pressure in right auricle in relation to the left one, the foramen ovale also closes. This is helped also by increasing pressure on left side. The heart rate is about 65/min in early embryo, but 140/min at birth.

Respiration: Respiratory movements do take place in the foetus (amniotic fluid seems to be aspirated into the lungs, because of this) The fluid is absorbed by lung tissue continuously and in large quantities. The onset of respiratory movements after birth, causes intense redness of skin within a minute after birth.

Nervous system: Peripheral reflexes are present from the 100th day of foetal life. But myelination of the tracts occurs only a year after birth. It is difficult to evaluate the functions of the nervous system, as the new born child has had no previous training to respond to external stimuli.

Digestion: Premature infants (born 2 months before full term) can digest and absorb food. The amniotic fluid is ingested and the dark tarry meconium found in the gastrointestinal tract at birth may be its residue mixed with excretory products of gastrointestinal tract.

Kidney: It does function during later months. Micturition occurs immediately after birth. Most of the amniotic fluid may be only foetal urine which is absorbed back by lungs and gastrointestinal tract, to eventually pass through the placenta into the mother's circulation to be excreted by her kidney. The amniotic fluid is isotonic with mother's tissues, and in early pregnancy, it may be formed by the amniotic membrane. It is replaced several times in a day.

Metabolism: It is similar to that of the mother. Storage of materials in foetal tissues, occurs for tiding over early post natal life. Calcium and phosphorus accumulate in foetus, the major portions of these in the last 4 weeks when rapid ossification of foetal bones with gain in weight, occurs. No ossification occurs till 4th month (X-ray evidence). Iron is concentrated in the endometrium prior to the implantation of ovum and it is phagocytosed by the blastocyst. Iron is also stored in the tissues of foetus for early post-natal use (milk is deficient in iron).

Vitamins: The role of vitamins is similar to that in adults. Vitamin B12 is required for erythropoiesis; vitamin D is not so much necessary, though it is stored in the liver prior to birth. Vitamin E is needed from the earliest stage of the embryo and is concerned with cell metabolism and division. Vitamin K is essential, especially in the early months after birth when intestinal bacterial flora are not developed for its synthesis.

Maternal Physiology in Pregnancy: The uterus increases in weight from 50 to 1000 gms. Uterine cavity of 2-5 cc in volume is enlarged to 5000-7000 cc. Hypertrophy is due to oestrogen. Breasts become double in size (mainly in first pregnancy). Vagina and introitus enlarge. Occasionally oedema and acne may be seen. Masculinising or even acromegalic changes may also occur.

Cardiovascular system: Due to the presence of the placenta, 1-1½ litres of blood will have to be diverted to it. The fall in peripheral resistance causes an increase in venous return and an increased cardiac output by 20-50% (cause - increased blood volume and increased metabolism). Cardiac output may fall to near normal value, several weeks before the end of pregnancy.

Blood and tissue fluid volume: These are increased by 20-30%, especially in later half of pregnancy. Increase is mainly due to corticoids, oestrogen and progesterone. At birth, the haemtocrit value falls due to hydraemia. Later, bone marrow produces more cells to counteract hydraemia. Before parturition, 1-2 litres of extra blood is present, about ¼th of which is lost, ordinarily, in delivery. The excess in blood volume provides considerable safety for the mother.

Weight gain: In the first few months, loss of weight may occur due to vomiting, but towards full term there is a gain of about 24 lbs – Foetus 7 lbs; amniotic fluid and membranes 4 lbs; uterus – 2 lbs; breast – 3 lbs and increase in body weight due to fluid – 8 lbs. After delivery, rapid diuresis and loss of fluid brings the weight down to the pre-pregnancy figure within a week or so. Both blood volume and that of tissue fluids diminish and normal weight is attained. Due to a craving for food during pregnancy and with uncontrolled eating, the weight increase may be even more than 24 lbs.

Metabolism: BMR increases slightly with increased heat production, and sensation of increased warmth is experienced. BMR rise is due to a greater hormonal output.

Diet: Even if mother has insufficient diet, foetus grows at her expense. The drain on the mother is more in later months and very great during lactation. Vitamin K may have to be added to the diet towards full term.

Respiration: Increased respiratory rate is seen in pregnancy. Owing to the pressure of abdominal contents, the movements of the diaphragm are diminished as also vital capacity. The rate of respiration has to increase to provide sufficient pulmonary ventilation.

Excretion: More or less normal or slightly increased. But, due to compression of the ureters by uterus, a predisposition to kidney infection (pyelitis) may occur.

Toxaemia: Rapid weight gain, oedema and hypertension due to excessive sodium retention by distal tubules, may result from excess hormonal production. Sodium deprivation alleviates the symptoms. Water intake need not be restricted.

Other changes in pregnancy: The mammary gland and nipple develop. Pigmentation on face, abdomen and areola around nipple, is seen. Predominance of anabolic processes with increase in BMR due to foetus, are concomitant features. Alkali reserve is diminished in pregnancy. Though physiologic compensated acidosis is said to occur, yet H-ion concentration is normal. Creatinuria occurs. Neutrophils increase in number

with rise in the erythrocyte sedimentation rate. Even glycosuria or lactosuria may occur, but this ceases after delivery.

Uterine movements in Pregnancy: Continued small rhythmic and regular and painless contractions of the uterus are seen from 2nd month. Intra-uterine pressure rises by 1-7 cms of water from basal pressure of 4-11 cms of water during contractions which are of frequency 1-2/min. The basal tone also shows slow oscillation. Contractions increase in amplitude as pregnancy advances, and especially in the last two weeks, and during labour, the force of contractions becomes very great because perhaps the uterus is increasingly sensitive to oxytocin, towards full term as a result of 1) gradual rise in oestrogen level and 2) decrease in progesterone level. Also, distension of uterus may make it more irritable.

PHYSIOLOGY OF LABOUR (PARTURITION)

Labour is the process by which the foetus and other products of conception are expelled, when pregnancy has reached full term. There are three stages in parturition — 1) Dilatation of cervix with rupture of membranes, 2) Expulsion of foetus, 3) Expulsion of placenta.

Pressures can be recorded by intra-uterine manometers, at various points in the uterus — upper, middle and lower parts. (Internal hysterography). In the first two stages, changes in amniotic fluid pressure can be recorded and they seem to be rhythmic due to uterine contractions. Increase in pressure may be as much as 30-60 mm of Hg. There is a basal tone of 10 mm of Hg (intra-peritoneal pressure). The contractions are 2-5 every 10 minutes, each lasting for 1-2 mts. Frequency and strength increase towards the end of 1st stage. In the 2nd stage, the abdominal muscles and diaphragm help. In the 3rd stage, placental blood pressure can be recorded. Uterine contractions occur with the same frequency and strength as in the first two stages and there is no quiet interval between the second and third stages. First contractions after birth are painless and a period of 5-15 mts. following foetal delivery has been considered as the physiological rest period, though contractions still go on but without the subject feeling any pain.

Optimum conditions exist for normal labour when contractions have an amplitude of 25 mm of Hg and fundus activity predominates and good synchronization between various parts of the uterus occurs, the contractions being rhythmic and regular. Two pace-makers, one on each side, at the opening of the fallopian tube, are present. Contractions travel down from them 1-2 cms every second and the whole uterus is covered in about 20 sec. Each pace maker may function alternately or one may predominate over the other. Contractions are more forcible at the fundus than lower down. Uterine contractions are per se not painful. The pain is due to cervical dilatation, perineal distension and vulval stretching with uterine ischaemia. Nervous factors, perhaps play little role in parturition. A denervated uterus can expel its contents but lumbar and sacral segments, if destroyed, will retard the labour process. A centre is thought to exist between 10th dorsal segment and 2nd lumbar segment, controlling labour movements. After labour contractions begin, dilatation process requires 18 hours for the 1st child and 12 hrs. or less for succeeding children (1st stage). Once cervix is dilated fully and membranes rupture uterine contractions decrease in severity, probably due to decreased irritability. But half an hour later or so, uterine contractions reappear. Once the head moves through the vaginal canal, the delivery is completed within a few minutes. During the different phases of labour—i. e. before and after cervical dilatation—contractions occur every 1-2 minutes and cause much pain due to uterine spasm and tearing of the birth canal. Reflex contractions of abdominal muscles occur and are superposed over uterine contractions. The force acting on the foetus is approximately 25 lbs. Contractions are intermittent. Otherwise foetal death will occur due to ischaemia of placenta. After the child is expelled, pains become less intense and uterus is greatly contracted. In the next 30-45 mts, renewed contractions occur and due to a shearing effect placenta is separated. Total blood loss due to this is about 350 cc (average). Uterine contractions prevent excessive loss.

Involution of Uterus: Within a week after parturition uterus involutes to half the size and in 4 weeks complete involution occurs if mother is lactating. Necrotic autolysis of placental site and that of uterine musculature gives rise to lochial discharge,

first bloody in nature and then serous, lasting in all a week and a half. After this, re-epithelization of uterine inner surface occurs. Preoccupation of anterior pituitary with release of prolactin (LTP) prevents early resumption of menstrual cycles during lactation. But, after several months GSH is produced in sufficient amounts to restart the sexual cycle.

Factors that bring on Labour :

- 1) **Progesterone block theory:** Progesterone produces myometrial block and it is greatest at the placental site. As the production of progesterone by the placenta ceases, the block is removed and the synchronous uterine contractions clinically manifested as labour pains, develop. Under the influence of progesterone, the concentration of water and sodium chloride at the placental site are diminished, whereas that of potassium is elevated. These changes tend to be abolished with the onset of labour. The changes in concentration of electrolytes, in turn, appear to inhibit the conducting mechanism of myometrium, with the result that uterus is incapable of synchronous activity, the prime requisite of effective labour.
- 2) **Hormonal theory:** During pregnancy, there exists a nice balance between the uterine stimulatory action of oestrogen and the uterine relaxing effect of progesterone. Towards full term, there is a drop in progesterone level, favouring the stimulating action of oestrogen. There is a great deal of controversy regarding this view. The uterine relaxing effect of progesterone itself is controversial. Oestrogen makes the uterine muscle increasingly sensitive to oxytocin and hence, as full term is reached, the oxytocic property of this hormone comes into play and labour sets in. (For further discussion see under neurohypophysis).
- 3) **Stretch theory:** Any hollow viscus tends to contract and empty itself when distended to a certain extent. As pregnancy nears full term, uterine enlargement slows down, whereas the rate of foetal growth increases. This results in rapid increase in intrauterine pressure. The resulting tension on the uterine muscle fibres may itself initiate labour. Further in 19 out of 20 cases, the protruding occiput of the baby acts,

as a wedge and brings about progressive dilatation of the cervical canal.

- 4) Mechanical irritation theory: The stretching of the lower uterine segment by the foetal head and the pressure exerted by it on the para-cervical nerve ganglia are probably important factors in the onset of labour.

CONTRACEPTIVE METHODS

The various methods used in contraception ('family planning') are directed at a single objective, namely the prevention of conception. In the case of abortion, destruction of the formed embryo is the result aimed at. Contraceptive measures mainly prevent the access of the sperm to the ovum. The actual methods vary in their approach in this respect. Tying or cutting the spermatic cord (vasectomy) altogether prevents the sperms from gaining entry into the female passage (vagina) from male genitalia. In the woman, ligation or tubectomy (tying the fallopian tubes or excision of the tubes) is the corresponding operation. Abolition of the production of sperms cannot be achieved, except by removal of both the testes or by exposure to X-rays, which measures are highly undesirable from many points of view. Immobilisation (preventing movement of the sperms, so highly essential for fertilisation) and inactivation can result from the use of spermicidal jellies smeared in the female passage. The use of condoms, diaphragm and other devices prevent the entry of the sperms, either from the male organ into the female or from the vagina into the uterus.

The use of the well-known loop or intra-uterine device (placed inside the uterus) is to prevent the embedding of the fertilised ovum in the uterus and thereby putting a stop to the growth of the embryo in the uterus.

The only two contraceptive methods which have any physiological basis worth discussion are the rhythm method (observance of safe period for marital relations) and that of oral contraceptives. The former is not at all popular and does not have many votaries, since the dice are heavily loaded against it. But its only merit is that it is the only truly physiological method and it is at least academically interesting to expatiate on, if not to implement in a practical way.

The Rhythm or the 'safe period' method restricts sexual union to the period of physiological sterility in each menstrual cycle. It depends on two facts: the ovum once liberated from the ovary is available for fertilisation only for 24 hours; the spermatozoon retains its ability to fertilise the ovum upto 48 hours after it enters the female genital passages. Thus, there is a minimum period of three days during which conception is theoretically possible and this should be the time interval in which there should be a taboo placed on sex relations.

It was observed by Ogino and Knaus that ovulation occurs, under ideal conditions, on the 14th day before the next bleeding phase, in the menstrual cycle. They allowed two days on either side for individual variation. Thus ovulation may come about between the 12th and 16th days counting back from the first day of bleeding of the next menstrual period. To the upper limit of 16, two more days may be added to protect against sperms deposited earlier. One day is to be subtracted from the lower limit of 12 to render the ovum released infertile. Thus, the days 18th to 11th, reckoning from the following bleeding episode, may be considered to be the fertile period and hence unsafe for contraception. For all cycles varying in length between 20 and 40 days, the period of fertility bears a constant time relationship to the onset of the following menstrual period. For computing the safe period, a woman should keep records for at least the preceding six months or preferably one year, in order to be in possession of reliable information regarding the length of her cycle. Only thus, she can know about the limits of her variation.

For example, in a subject whose shortest and longest cycles are 25 and 32 days respectively, the safe period would last till the 7th day (25-18) from the date of previous bleeding and recommence after the 21st (32-11) day. Charts have been prepared showing the extent of the safe period for all cycles from 20 to 40 days. This method is bedevilled with many difficulties. Only a woman with the greatest zeal for this method can pursue it with any degree of success and even then only if she exercises unremitting vigilance. The changing length of the menstrual cycle, which is capricious, is the greatest impediment to the

success of this method. Also, the procedure is utterly ineffective in people with very short cycles of less than 20 days and also when the cycles vary by more than 10 days, frequently.

One practical means of overcoming the hazards due to the erratic variation in the length of the cycle is to pinpoint the actual day of ovulation by recording the basal body temperature. A rise of about 0.6°F occurs at the time of ovulation and this could be detected, provided meticulous precautions are taken to eliminate fortuitous causes of a rise in temperature, such as muscular exercise and fever. The temperature is taken in the morning, with the woman at complete rest for at least an hour prior to the taking of the temperature. Even so, preliminary training from a doctor, in the use of a thermometer, may be found desirable to avoid pitfalls. Sometimes, there may be more than one rise during the course of a cycle and this will completely misguide the person as to the exact time of occurrence of ovulation. Ironically, in non-ovulatory cycles, there will be no rise of temperature at all, compelling abstinence in a totally safe cycle. Though there are two other ways of detecting ovulation, they are unfit for use in domiciliary practice. A new test arises from the fact that the uterine cervical glands secrete glucose at the time of ovulation and this can be revealed by applying a strip of enzyme paper to the cervix. But even this cannot be done by the woman herself and the test is vitiated by the secretion of glucose by vaginal glands even in the absence of ovulation.

One of the major drawbacks of the rhythm method is that it imposes a restraint on the married couple for part of the duration of the menstrual cycle and in highly sophisticated and permissive societies, this may lead to break up of marriages. Much more important than this is the risk of ectopic (outside the uterus) pregnancies and placenta previa (placenta blocking the cervical passage). Also, the possibility of embryonic abnormalities, consequent on an aging ovum or a deteriorating sperm outliving its viable period and taking part in an unforeseen conception resulting from intercourse outside the 'fertile' period, cannot be ignored. In populations in the West favouring this method, a higher incidence of anencephaly and spina bifida has been observed. On the contrary, among the races given to traditional practices, there is a low rate of foetal abnormalities and these sects practice total

abstinence for seven days after menstruation and sexual union, when desired for the sake of progeny, is confined only to the anticipated date of ovulation. This is proof positive that foetal anamolies are sometimes a tragic by-product of this method.

The rhythm method, because of all these shortcomings, has been described by de Bethune as a source of mental torture in matrimony.

ORAL CONTRACEPTIVES

The final word has not yet been said as to the exact mode of action of oral contraceptives. The notion of using certain hormonal preparations administered by mouth as a contraceptive procedure, originated in the suggestion by Beard in 1897, that the corpus luteum of pregnancy inhibited ovulation, once conception had occurred. The phenomenally rapid strides in gonadal physiology has made it possible now to use various synthetic analogues of the female sex hormones, oestrogen and progesterone, in preventing ovulation and thereby eliminating even a remote chance of conception altogether, as long as it is desired, in the life of a woman. Logically, progesterone should be the contraceptive hormone of choice, as it prevents ovulation, by itself. All the same, oestrogen has also been used for certain reasons. This hormone, when present in sufficient concentration in blood, inhibits by a negative feedback, the release of the follicle stimulating hormone (FSH) by the anterior hypophysis. FSH, as is well-known, promotes the development of the graafian follicle culminating in ovulation and in fact, can even cause super ovulation—the liberation of more than one ovum, sometimes. Thus, oestrogen can indirectly prevent ovulation. Continuous administration of progesterone, as pointed above, also keeps ovulation at bay and in addition, it suppresses the secretion of the luteinising hormone LH, which according to some authors, is actually responsible for ovulation. Therefore, the use of progesterone seems to be on a sound basis. It has been further noted that synthetic hormones are even more potent than natural ones. The main aim of the use of these oral preparations is directed against the release of pituitary gonadotrophins and thereby avoiding ovulation. Surgical laporatomies have demonstrated the suppression of ovulation under contraceptive regimen

and urinary assays have shown irrefutably the absence of the midcycle peak of oestrogen titre and also that of the excretion of pregnandiol during the luteal phase. There is also no rise of temperature indicative of ovulation.

As a bonus, steroid therapy confers two more advantages. The character of cervical mucous is altered so that it is inimical to the survival of sperms in the female passages. Motility of the fallopian tubes is diminished, thus further hindering the transport of the ovum, if by any chance it is released by the ovary.

The high lights of the use of oral contraceptives are that no irreversible alterations occur either in the female genitalia or in the endocrines even after prolonged administration. Unlike surgical procedures which more or less drop a curtain of finality over future prospects of begetting children, steroids leave the woman unscathed, ready to conceive at any future day, if she desires to have issues.

One apparently physiological method of minor importance is to suppress spermatogenesis by raising the temperature of the scrotum. In the State of Maharashtra, subfertility has been noticed among men who wear tight scrotal suspenders throughout the day and sometimes for many days at a stretch.

A word about restoration of fertility by recanalisation after vasectomy – in an Indian study of a series of 76 cases, 63 men were found to have sperms in their semen and 42 of them became fathers.

THE BREAST AND LACTATION

The breast, phylogenetically, is related to the brood spot in the birds. Mammals are so called because the mother suckles her young ones at her breast (mamma).

The breast is a subcutaneous gland. Groups of alveoli discharge their contents into small ducts which join other ducts from neighbouring alveolar clusters to form lactiferous ducts, a number of which converge towards the nipple, a rounded or conical elevation with some amount of plain muscle tissue in it. Each duct has a dilatation (the ampulla which holds some quantity

of milk ready for ejection) proximal to its opening at the surface of the nipple, which itself is covered and also surrounded by the areola, an area of dark or pigmented skin. The entire breast has quite a large amount of adipose tissue in between the lobules of the gland as well as covering the entire gland and it is responsible for the normal smooth and hemispherical shape of the adult female breast.

Placed in the walls of the ducts and also between the basement membrane and alveolar epithelium, are the star-shaped myoepithelial cells which on stimulation contract and squeeze out the milk from the alveoli into the ducts and from the ducts to the exterior. The hormone, oxytocin, is the physiological excitant to these cells.

It must be pointed out that the male breast is a rudimentary gland, as it is in the pre-pubertal girls. Rapid development of the female breast occurs by the proliferation of the ducts and alveoli at the time of puberty. Thereafter, the breast undergoes some degree of development during each menstrual cycle and probably a little regression in between two cycles. The maximum development occurs during the first pregnancy. Fatty tissue also increases in amount gradually. A number of hormones influence the development of the breast as well as its secretory activity.

The ovarian hormones oestrogen and progesterone are primarily responsible for the stepwise development of the breast which begins at puberty, on account of the monthly sex or menstrual cycles which commence at this time. Oestrogen stimulates the growth — lengthening and branching — of ducts along with an increase in their diameter, increase in the stroma of the breast and deposition of fat. All these changes occur during the follicular phase. During pregnancy, however, these changes become accentuated, in the presence of larger amounts of oestrogen released from the placenta.

During the luteal phase, progesterone acts on the breast which has been primed for its action by oestrogen which was effective in the proliferative or follicular phase. The growth of lobules, and of the alveoli and the onset of secretory changes in the cells are the consequences of progesterone action.

The pituitary and the development of the breast: In lower animals, prolactin or the luteotropic hormone exhibits synergism with oestrogen and progesterone in its influence on the breast. It is perhaps reasonable to assume such a role for human prolactin too, though it has been considered to have a profound influence in also initiating milk secretion (lactogenesis) after parturition. The low levels of oestrogen in the later months of pregnancy provoke the pituitary to put forth prolactin which brings about the secretory activity of the breast. During pregnancy however, progesterone is thought to have a depressing or antagonistic action on prolactin. At the time of parturition, progesterone level falls and oestrogen has an unimpeded action in eliciting prolactin release from the pituitary. Milk secretion is thus initiated. Oestrogen in large or therapeutic doses, inhibits milk secretion and has been used in the form of stilboesterol to suppress lactogenesis when it becomes unnecessary, as in the event of death of the newborn.

The placenta, by its output of oestrogen and progesterone during pregnancy, maintains the development of the breast, since it is the only tissue elaborating these hormones in this period. Removal of placenta, as may occur in abortion, causes regressive changes in the breast. It is necessary to emphasize that nervous influences play no part in the development of the breast, contrary to the views of some Russian workers.

In the first pregnancy, the skin of the areola which was previously rose in colour, acquires pigment and becomes dark in appearance and this is a permanent change.

Milk secretion (Lactation): This is described as occurring in two stages — 1) Lactogenesis or the commencement of milk secretion 2) Galactopoiesis or maintenance of secretion.

The initiation of lactation seems to take place even before parturition. It is the free flow of milk that is possible only after the expulsion of the foetus and even this occurs in full measure only a few days after parturition. Prolactin is the key hormone of this phase of lactation and oestrogen in physiological amounts is the provocative stimulus for the release of prolactin.

Galactopoiesis seems to be due to an interplay of several hormones. Growth hormone (somatotrohin) and thyroxine are the most potent of the hormones in galactopoiesis. The former provides fat for deposition in the gland by the conversion of glucose. The other hormones may also facilitate galactopoiesis by their specific physiological actions.

Ejection of milk: When the infant, soon after birth, suckles at the breast, not much flow of milk occurs immediately, but a few moments later a copious flow results. This is due to a neuro-humoral reflex. The act of suckling at the nipple sets up impulses which are conveyed to the hypothalamus through which the neurohypophysis is made to release oxytocin. This hormone is conveyed in blood to the breast where it excites the myo-epithelial cells to contract and eject milk.

It is a common experience that when a cow is milked, in the beginning, there is very little flow of milk but shortly thereafter, milk flow increases enormously and this phenomenon was formerly attributed to a mysterious 'let down' factor which is now identified as oxytocin. Injection of oxytocin into cows and into isolated udders increased the milk flow. It has been used in medicine in bringing about emptying of breasts which are painfully engorged with milk.

Lactation, while it hastens involution of the uterus, may delay the restoration of the menstrual cycles after the amenorrhoea of pregnancy. The latter effect is doubted by some.

It may be mentioned that emotional upsets may interfere with the flow of milk by preventing the release of oxytocin, as has been observed in animals. The yield of milk in cows may diminish even if the surroundings are not congenial. These facts are sufficient to impress upon the importance of emotional influences on the output of milk.

The composition of milk: Milk is nearly as complex a fluid as blood itself. It is an ideal food for the newborn as well as the infant, since it contains all the food ingredients necessary for the health and growth of the baby or the young animal.

The secretion that occurs in the first few days after the birth of the baby, known as colostrum, is yellow in colour with a high protein and salt content. Large cells — colostrum corpuscles—loaded with fat are seen in this fluid. They may either be epithelial cells of the breast alveoli or white blood cells.

The milk of the early weeks after parturition is also of a special kind called the intermediate or transition milk. Typical milk, as the term is understood, is formed only after a month, after the birth of the child. The accompanying table shows the average composition of human and cow's milk.

	Cow's Milk	Human Milk
Carbohydrate (as lactose)	5.0	7.0
Protein—Casein	2.5	1.0
Lactalbumin	0.7	0.4
Fat	3.5	4.0
Calcium	0.14	very little.

(Figures indicate gms. per cent and have been rounded off as far as possible).

Colostrum contains about 8.5 gms. per cent of protein.

Certain significant points arise from comparison of cow's milk with human milk.

1. Human milk has more sugar and is hence more palatable.
2. Human milk is naturally more suitable for a human infant since it has less protein and this facilitates digestion. Cow's milk forms a tough curd (casein) in the stomach and the infant's stomach may not be able to digest it. There is much more caseinogen in cow's milk.

Milk is deficient in certain respects.

- a) It is poor in iron. So there is a necessity to supplement milk with iron.
- b) Vitamin C, in view of its low content in milk has also to be given separately. Milk has adequate quantities of vitamins A, B and D.

Sources of milk constituents: It is remarkable that the glandular epithelium, though apparently consisting of only one

type of cell, can synthesise out of the blood constituents, a variety of substances for incorporating in milk. The glandular cells resemble the hepatic cells in their versatility.

1. Lactose is derived from blood glucose.
2. The plasma proteins and free amino acids yield milk proteins.
3. Milk fat is synthesised partly from neutral fat of the blood and organic radicles like acetate in the blood.

The composition of milk may to some extent be determined by the diet of the mother. Illness and psychological factors may seriously change the composition. The lactating mother should be on an adequate and nutritious diet to enable her to pass on to the offspring all the necessary food ingredients in the milk. Even if the mother's diet is deficient, the breast removes (by way of milk) sufficient quantities of materials from the mother's body stores, for the use of the baby and thus depletes her reserves. Many drugs administered to the mother are excreted in the milk and care has to be exercised in prescribing them for the mother.

Milk secretion by the breast is an active process requiring the supply of energy.

The female breast in old age: Atrophic changes take place after menopause. The fatty tissue diminishes and fibrosis occurs. There is shrivelling of the entire breast which becomes pendulous.

Gynaecomastia: This is a condition wherein the male breast enlarges though not to the size in the female. Treatment with female sex hormones for certain conditions may set up this abnormal development. Spontaneous development may occur on account of hormonal imbalance.

Witch's milk: In the first few days after the birth of the baby, milk secretion may occur in the newborn. This is held to be due to the oestrogens of the mother passing on to the baby and bringing about the release of prolactin in the latter. Thus, the baby's breast is said to be excited, leading to the formation of milk.

NEUROPHYSIOLOGY

While introducing the subject of endocrinology, a reference was made to the two controlling systems for the regulation of the various bodily functions, viz - nervous and hormonal. The former is precise in its direction and magnitude, quick in onset and cessation of action. Nervous system phylogenitically is at a higher level than the endocrinal system.

The view that the complex mass of nervous tissue is made of innumerable anatomically independent though physiologically interdependent units called neurones (neurone theory), arose out of the fundamental studies of Ramon Y Cajal on nervous tissue. Complementary to this is the opinion of Golgi who visualised the nervous system as a complicated network. These two pioneers were jointly awarded the Nobel Prize.

Nervous system consists of myriads of nerve cells and these are supported and held in position by neuroglial cells. The latter are said to be of three kinds.

- a) Astrocytes - these are cells with innumerable processes and they seem to form the so called blood-brain barrier.
- b) Oligodendroglia - have as the name suggests, few processes. Their function may be concerned with providing myelin material to invest nerve fibres. This may prevent cross excitation of one nerve fibre by another.
- c) Microglia - These are usually included in the family of reticuloendothelial cells. Phagocytosis is a property attributed to these cells.

Whenever a nerve cell dies owing to disease processes or injury, it is replaced not by a new nerve cell but by neuroglial cells.

THE NERVE CELL AND NERVE FIBRE: Nerve cells proper are classified in different ways. One such is a twofold division into Golgi type I and type II cells. The former are present in the grey matter and their axons are long and enter the white matter and are projected to different parts of

the brain or even to peripheral destinations. Type II cells are those which are confined entirely to the grey matter. Alternatively, neurones are identified by the number of processes in the cell – unipolar, bipolar and multipolar represented respectively by the cells of the mesencephalic nucleus of the V nerve, bipolars of retina and anterior horn cells of the spinal cord. Some special types of neurones are seen in certain parts of the brain, like the large Purkinje cells of cerebellar cortex with all their dendrons ramifying in a single plane like ivy (a creeper) on a wall.

The nerve cell or neurone is perhaps the most specialised or differentiated of all cells in the body. It lacks a centrosome and so cell division is not possible. The number of neurones is fixed at birth. As age advances, the number may be reduced, dead ones being replaced by neuroglia. The cell processes lengthen with skeletal growth in order to keep in touch with their terminal organs. The number of internodes and nodes of Ranvier does not change, the internodal regions elongating with growth.

A nerve cell (Fig 38) is made up of a cell body or perikaryon and two kinds of processes. Dendrons or dendrites conduct impulses towards the cell body and these may be one or more in number. The single axon is the only process which transmits impulses away from the cell body and it arises from an elevation on the cell surface known as the axon hillock. There are a few intracellular structures which can be made out by special staining, though there is a certain amount of uncertainty as to their presence as such, in a living nerve cell. Even so, the same histological techniques reveal such structures in all nerve cells and the arrangement of these intra-cellular elements being almost the same in all. It is therefore reasonable to conclude that they are present in the form in which we see them in all histological preparations. Among these are Nissl's bodies, neurofibrils and the superficial and deep endoplasmic networks of Golgi. It is however not possible to demonstrate all the structures in one preparation, for one histochemical technique brings out only one kind of internal feature, while obscuring the others. Nissl's granules have an avidity for basic stains and are of a spindle shape. Each exhibits many narrow, parallelly arranged and membrane

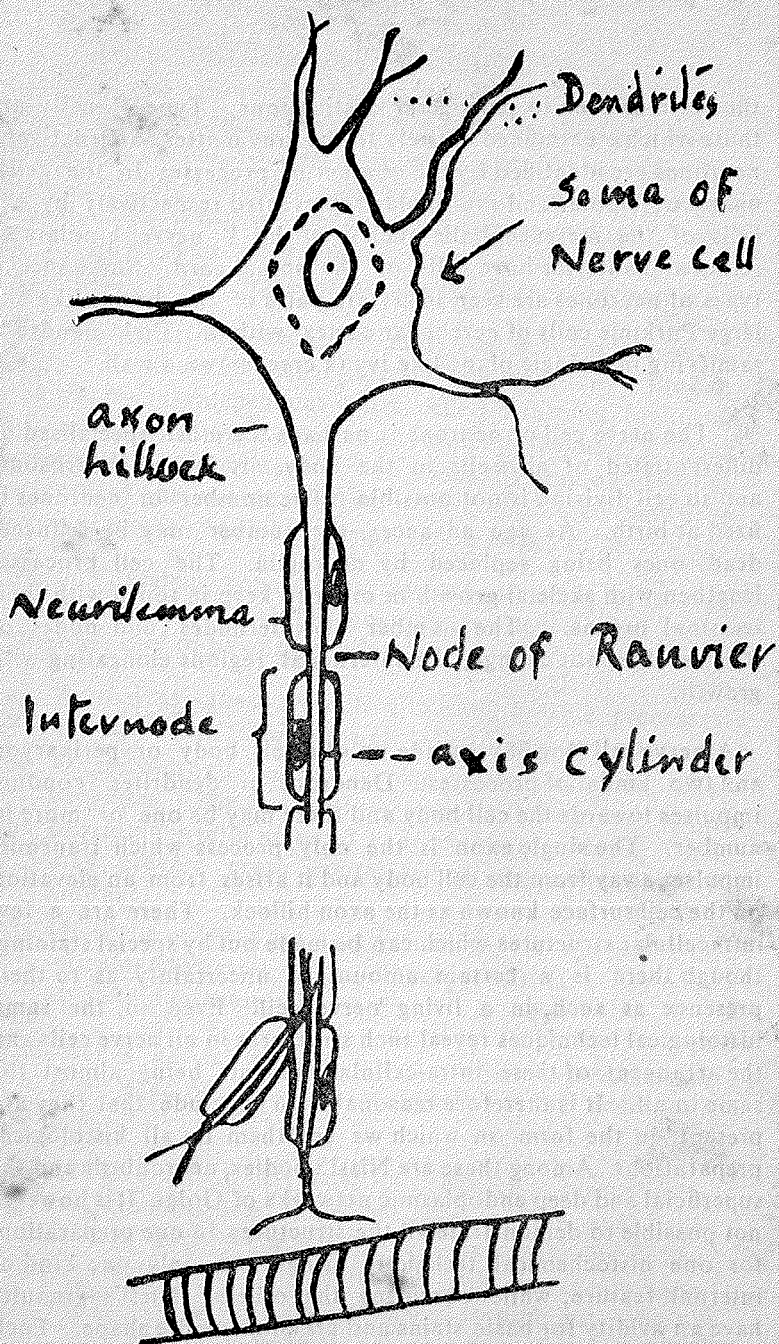


FIG. 38 THE NERVE CELL

enclosed cavities, their external surfaces presenting many small particles said to be formed of ribosenucleic acid. Protein synthesis seems to be the function of these structures. When the nerve cell suffers injury, Nissl's granules undergo disintegration into fine particles, this being known as chromatolysis. Neurofibrils are thin filamentous structures running through the cell body from the dendrites towards the axons which they enter. Their physiological role is yet to be elucidated. Two kinds of cytoplasmic network or reticula also have been demonstrated—a superficial one and a deep or endoplasmic one named after Golgi.

Nerve cells differ in the number of dendrites but all have only a single axon each. This process arises from a prominent part of the cell body (axon hillock) which is, strangely, devoid of Nissl's granules. As the axon enters white matter after leaving grey matter, it comes to be invested with a myelin sheath. Myelin is composed of lipids and is electrically non-conducting. Thus, it insulates one axon from the others, making cross excitation impossible. While sensory fibres seem to be myelinated at birth, motor fibres are only gradually covered with myelin and this process is completed only by about two years of age of the baby. Muscular coordination as required for walking is probably dependent on the presence of myelin around the motor axons.

As a myelinated fibre leaves the central nervous system, it acquires another covering—the neurilemmal sheath formed by cells of Schwann, which seem to be wrapped around the axon, as it were. At regular intervals the myelin sheath is absent where the neurilemma comes to lie next to the axon or axis cylinder. Such regions are known as Nodes of Ranvier, the portions in between two neighbouring nodes being called internodes. Only one cell of Schwann provides the neurilemmal covering for each internode. Its nucleus can be seen on one side of the axon just inside of the boundary of the neurilemmal coat.

Each nerve fibre has one more protective layer of connective tissue—viz—endoneurium. A bundle of such fibres is demarcated by a perineural envelope, the whole nerve trunk is in turn covered by epineurium.

Effects of injury to a nerve cell and nerve fibre :

A nerve cell if injured or affected by disease will die, the void being filled by neuroglial cells. When a peripheral myelinated

fibre is injured, recovery is possible and repair ensues. Damage may be caused by mere compression of the axon (axonotmesis) or complete severance of the nerve fibres with its coverings (neurotmesis). In the former case, recovery is rapid. Structural changes may not occur at all. In the case of complete division, certain characteristic changes occur in all the structural elements of a nerve cell. Originally these were described for the segment of the nerve fibre peripheral to the site of injury and the term Wallerian degeneration was applied to this. Later, it was seen that similar changes occurred proximal to the point of section and even involved the soma or the cell body. The same term has now been extended to all these features. The sequence of events following injury to a nerve is best described with reference to an injured motor nerve.

The earliest sign (after 24 hrs) of damage, to appear is the tortuosity of the axis cylinder which very soon breaks up into constituent neurofibrils which themselves further break into short fragments and ultimately disappear. Myelin material shows degeneration, resulting in the formation of ovoid masses retracting from the nodes. Following this, further changes occur causing decomposition of the myelin into Kephalin and Lecithin. The latter breaks down before finally being absorbed, to choline, glycerophosphates and unsaturated fatty acids. The last named component can be demonstrated by Marchi's method of staining with osmic acid and potassium dichromate. This is a very useful procedure and has been of great help in determining the course of nerve fibres. The cells of Schwann proliferate and some even take on phagocytic properties to clear away the products of the breakdown.

In the central segment, same changes as described above are seen extending upto the first node of Ranvier. The cell body (48 hrs) becomes cloudy in appearance and the nucleus may be pushed to one side or even extruded from the cell causing its death. Nissl's granules disintegrate (chromatolysis) and even disappear. If recovery occurs they reappear.

Within about 20 days or so, the products of decomposition are all removed by phagocytes and what remains is the empty neurilemmal tube of the central and peripheral segments. When

the debris has been cleared, the axon starts growing from the first node of Ranvier at the rate of one to two millimeters per day, along the neurilemmal tube of the proximal segment. When it reaches the open end of the neurilemmal tube of the distal segment, it grows into it to reestablish contact with the original effector organ. If entry into the neurilemmal tube is prevented as happens when there is much scar tissue at the site of injury or the two cut ends have moved away from each other, regeneration cannot take place. Suturing the cut ends, preferably performed at the time the debris has been removed, will facilitate regeneration which is completed in two or three months or more depending on the length of the nerve fibre. The regenerated fibre however, does not attain the full thickness of the nerve fibre before injury, nor is the previous velocity of conduction fully restored.

It has been observed that if two cut ends belonging to different kinds of nerve fibre eg. cholinergic and adrenergic or motor and sensory, are sutured, regeneration will not occur. But the central end of one motor nerve can be joined to the peripheral portion of a different motor nerve to restore the function of a muscle. This has been in vogue as a surgical measure in restoring function of muscles paralysed as in poliomyelitis or leprosy.

The progress of degeneration in a nerve fibre (a motor fibre) can also be watched by noting the responses to electrical stimulation, of the nerve and the muscle. In the early part of the process, the nerve fibre loses its responsiveness to faradic stimulation and still later, its response to galvanic stimulation will alter giving rise to an abnormal effect in that the muscle innervated by the degenerating nerve will exhibit a slow wormlike contraction. Finally the nerve becomes completely inexcitable before regeneration occurs. As the nerve degenerates, the muscle fails to respond to direct faradic stimulation owing to increase in chronaxie and later, it becomes somewhat hyperexcitable to galvanic current, the effect however being qualitatively different from a normal one. The state in which, the nerve is excitable for galvanic current but not for faradic form and the muscle is relatively inexcitable to a faradic stimulus, is known as the partial reaction of degeneration. Subsequently, the nerve completely becomes unresponsive to any form of stimulation, the muscle retaining only an abnormal sensitivity to continuous

current and this condition is referred to as complete reaction to degeneration. Collectively, all the features mentioned above are called the *Electrical Reaction of Degeneration*.

A muscle can be stimulated in the intact body through its motor point which is the surface marking of the point of entry of the motor nerve trunk into the muscle. The stimulating electrode which has to be placed on the motor point can either be the anode or the cathode of the electrical circuit, the other electrode (indifferent electrode) placed on a part of the body surface far away from the motor point. When the anode is the stimulating electrode and continuous current is switched on, a twitch of the muscle is elicited at the closing or making of the circuit (Anodal closing contraction - ACC) and another at the opening or breaking of the circuit (Anodal opening contraction-ACC). Similarly, a cathodal closing contraction (CCC) and cathodal opening contraction (COC) could be obtained. These twitches are in the following order of magnitude in the normally innervated muscle.

$$CCC > ACC > AOC > COC$$

When the motor nerve is degenerating, the above relationship is reversed as follows :- $ACC > CCC$.

It has to be noted that the neurilemmal covering is necessary for regeneration. Only peripheral nerves recover after injury. Because of the lack of this covering, tracts in the central nervous system will not regenerate. The optic nerve is really not a nerve but only a tract of the brain and consequently injury to it results in permanent damage.

Transneuronal Degeneration : While degeneration of a fibre is the natural sequel to injury, sometimes nerve cells on which the injured fibre ends in a synaptic contact will show signs of degeneration. Such a change is seen in the cells of the lateral geniculate body when the optic nerve fibres are sectioned. This is known as *Transneuronal degeneration*. The underlying cause of this has not been understood. It is possible that all the afferent fibres to the lateral geniculate body are derived from the optic tract and interruption of this may render the cells of the geniculate body functionless and a disuse atrophy may follow. Alternatively,

the optic tract may exert some trophic action on the lateral geniculate cells which atrophy in the absence of the trophic influence.

Nerve cells, along with glandular elements and muscle fibres, form the trio of excitable or irritable tissues in the body. This responsiveness to stimulation of various kinds, especially that of the electrical type, has been studied in detail. Certain aspects of this property of excitability will now be discussed.

RESTING MEMBRANE POTENTIAL: The nerve fibre is enclosed all round by what has come to be known as *Electrical membrane*, since at first, its existence was inferred only by its electrical properties. It cannot be seen with the light microscope. Recently, the use of the electron microscope has revealed its presence. It is about 100 Angstrom units in thickness and consists of one or two units, each of the following composition.

- 1) Protein molecular layer outermost.
- 2) Lipid molecular layer—2 rows of lipid molecules with nonpolar ends opposed.
- 3) Inner layer of protein molecules.

It has a high electrical resistance and it acts as a nonconducting (dielectric) medium separating the highly conductive extracellular and intracellular fluids. It is, normally, almost impermeable to cations like sodium, potassium, calcium and Magnesium, while allowing small anions like chloride, phosphate and bicarbonate to diffuse across freely. The knowledge regarding the membrane potential, originated from the postulations of Bernstein who put forward basic ideas concerning the maintenance of the resting membrane potential. According to him, the membrane separated positive charges (outside) from negative charges (inside). The actual ionic basis was elucidated by Hodgkin and Huxley who used the glass microelectrode (of less than one micron width at the tip and not visible under light microscope) filled with potassium chloride solution. The invention of the microelectrode was made earlier, but these two workers used it to impale the giant squid axon (1 mm in diameter) which was not damaged by the entry of the electrode. A direct measurement of the membrane potential was made by them, for the first time. Such studies have since been extended to mammalian tissues

also. The findings and conclusions of Hodgkin and Huxley form the basis of the following discussion on membrane potential. In the resting condition of the nerve, there is a potential difference between the exterior and interior of the nerve fibre, around 80–90 mv, the inside being negative with respect to the outside. This has been called the resting membrane potential. A calculation of the 'equilibrium potential' for the different ions present on both sides of the membrane, based on their actual concentrations and in accordance with the well known Nernst equation, shows that the actual resting membrane potential, as measured by an intracellular microelectrode, is approximately the same as the equilibrium potential for the potassium ions (more inside than outside). The sodium ion does not determine the resting value. Hodgkin and Huxley conclusively demonstrated that alterations in the external and internal concentrations of potassium ions brought about changes in the value of the membrane potential. The close agreement between the observed value and the calculated values, left no room for any doubt. The slight discrepancies that were seen were attributed to the minor role of other ions.

ELECTROTONUS: This term refers to the changes that occur in a nerve at the positive and negative terminals placed on it with a continuous current flowing through it. Before the classical studies of Hodgkin and Huxley, the physical basis of electrotonus was a mystery. But now it can be explained on the basis of the cable properties of a nerve fibre which has a highly conducting interior or core which is separated from the highly conductive exterior (extracellular fluid) by the electrical membrane of great electrical resistance. The nerve fibre resembles a trans-oceanic cable laid on the bed of the sea. As current flows from the positive terminal across the nerve membrane, through the core of the fibre and again across the membrane back to the negative terminal, the membrane potential of *the region under the two poles* suffers changes. At the positive terminal, there is hyperpolarisation or increase in the potential difference between the exterior and interior and under the negative terminal, the potential difference is reduced (depolarisation) which reduction if carried on to a sufficient degree (threshold) will generate an impulse. In other words, the resting membrane potential not only approaches the zero potential level (both sides of the membrane at the same

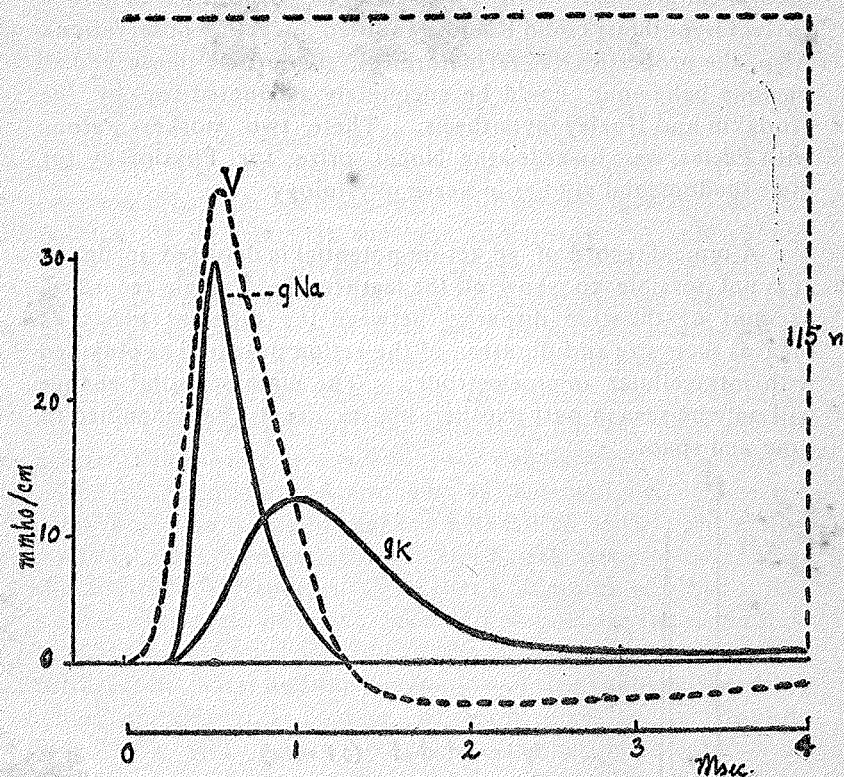
potential), but overshoots it to bring about a reversal, the outside becoming actually, though temporarily, negative in respect of the interior. It will be seen from this, that the state of depolarisation even if it be to a subthreshold level, will make the cathodal region more susceptible or sensitive to a *α* superadded or extra stimulus which will cause depolarisation with greater facility than when acting by itself. In other words, the cathodal region becomes more excitable than normally. On the same grounds, the anodal region becomes even less than normally excitable because of the hyperpolarised state. This is one of the features of electrotonus. On the same token, the conductivity for an impulse will be diminished at the anodal region and enhanced at the cathodal region. This will be better understood when the mechanism of the conduction by a nerve is described later. To sum up, the electrotonus at the anode (anelectrotonus) will be manifested as lowered excitability and diminished conductivity. Contrarily, catelectrotonus signifies heightened excitability and enhanced conductivity. There is however, a point on the nerve situated between the anode and cathode, at which the two effects are completely balanced against each other, this being the indifferent point which is nearer the anode when the polarising current is weak but moves towards the cathode and comes very near it when current strength is raised gradually. The region of catelectrotonus or anelectrotonus extends in both directions along the nerve from the cathodal and anodal regions respectively. Thus, if a point in the region of anelectrotonus is electrically connected with a point in the catelectronic area, current flow is established from the former to the latter. When the flow of externally produced current in the nerve is stopped, the changes in the excitability and conductivity at the two regions will be reversed, excitability and conductivity heightened at the anode but being depressed at the cathode. This is called the *resolution of electrotonus* and means the reversal of the state of electrotonus.

If, of two electrodes (in an electrical circuit) placed on the motor nerve to a muscle, the anode is nearer the muscle, then the current thus flowing is called ascending current. If the cathode is nearer the muscle, the current is said to be descending. Certain facts have been noted in this regard. With strong descending current, excitation of the muscle occurs only at the make of the circuit and the impulse will be

conducted to the muscle. This is so because, resolution of catelectrotonus at break is so strong that it will completely block the impulse arising at the anode. With strong ascending current, contraction of muscle occurs only at the break, as a block will develop at the anode at the time of make. With weak descending or ascending currents, excitation occurs at the make of the circuit only, since the rise of catelectrotonus is more effective than the fall or resolution of anelectrotonus. These findings are grouped together and go by the name Pflüger's laws of contraction.

Excitation of a nerve fibre and action potential: In the context of electrotonus it has already been mentioned that when depolarisation progresses to the threshold level, the excitation of the nerve membrane occurs. At the region of the cathode, the outward passage of the polarising current tends to disturb the membrane potential towards depolarisation. If the threshold value is attained, a vicious circle is set up. Even a slight depolarisation will alter the membrane permeability; permitting the entry of Na^+ (much more outside than inside) into the fibre which, in its wake, causes further depolarisation. With consequent influx of more Na^+ into the fibre, the membrane potential becomes unstable at the threshold level. On account of the invasion, as it were by Na^+ ions into the interior, it rapidly attains the value that falls just short of the equilibrium potential for Na^+ as calculated for Na^+ concentration at resting condition. Even so, the membrane potential is not held at the new level except very transiently and it drops back to its resting value in less than a millisecond. Even before the peak value of the potential change is reached, the permeability of the membrane to Na^+ starts to diminish and moreover, K^+ from now on leaks out at a faster and faster rate. Consequently, the full value of Na^+ equilibrium potential is not attained and the change is reversed to re-establish the resting potential. The sequence of all these changes is represented in the record of the action potential which is due to the transient reversal of the membrane potential. (Fig. 39)

In the early part of this century, Bernstein put forward his ideas on the mechanism of impulse generation in the nerve. According to his conception, the depolarised membrane becomes permeable to all ions and consequently the resting membrane potential



g_{Na} - Sodium Conductance, g_K - Potassium Conductance
 V - Action Potential (calculated)

Fig. 39

(After Hodgkin, Proc. roy. Soc., 1958, B 148:1 - 37)

attained zero value — both sides of the membrane are equipotential. This view does not explain the reversal of the membrane potential as observed by Hodgkin and Huxley whose conclusions and explanations based on sodium ion movements, adequately cover all aspects. Alterations in the external concentrations of Na^+ modified the extent of the overshoot above zero level as expected on the basis of the Nernst equation. Further experimental proof has been provided by these workers in support of their hypothesis. Using radioactive Na^+ , Hodgkin and Huxley determined experimentally, the amount of Na^+ influx per impulse and this was of the same order as that obtained by calculation on

theoretical grounds. This is a classical demonstration of how a correct hypothesis could be substantiated by actual observations. Also, the properties like refractoriness, subnormal phase and all or none behaviour, could be adequately accounted for by the Hodgkin and Huxley hypothesis. These two workers, along with Eccles, were awarded the Nobel prize for Physiology for their fundamental studies in nerve physiology.

A typical record of an action potential is depicted in fig. 40. It is not possible to show all the features in a single record on account of the wide disparity between the different phases as regards their size and duration of the action potential as obtained with intracellular microelectrodes. The main potential change will only be seen in part if other phases are to be magnified in time and space.

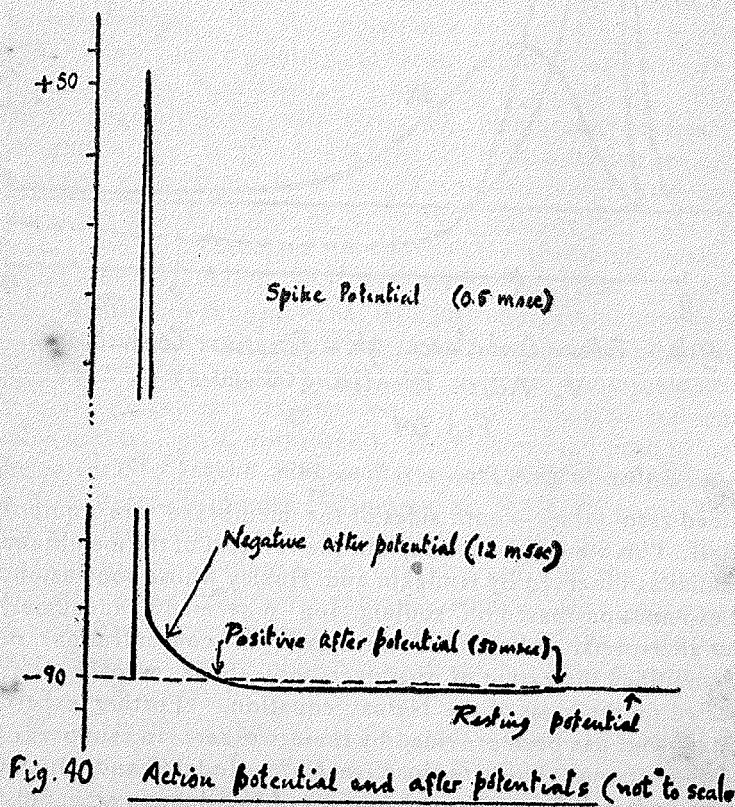


Fig. 40 Action potential and after potentials (not to scale)

The changes in the excitability of the nerve fibre have been correlated with the phases of the action potential.

All or None response of nerve fibres: It will be evident from the foregoing discussion that if the membrane potential is displaced to the threshold level, further change will occur progressively and spontaneously till actual reversal occurs. All that is necessary is that the polarising current should be of just sufficient strength to displace the membrane potential to the threshold value, an action potential then being set up as a matter of course. The height of change — the amplitude of the action potential — is determined only by the concentrations of Na^+ outside and inside and by no other factor. The strength of the polarising current need not be greater than the one just necessary to depolarise the membrane to the threshold level. A stronger current will also achieve the same objective and a weaker one will fail to set up an action potential since the depolarisation will be at a level below that of the threshold. Hence it follows that a stimulus whether of just minimum strength or above, need only depolarise the membrane to the threshold level and beyond this, it has no influence on the further time course and the magnitude of the action potential. Thus, an effective stimulus, whatever may be its absolute magnitude, will cause the setting up of an action potential of an invariable size under a given set of conditions. Stimuli which are weaker cannot give rise to an action potential at all. Thus, the stimulus either fails to activate the membrane or does so to the maximum possible extent which does not depend on the strength of stimulus but on the Na^+ concentration in the external fluid.

Recording of the action potential: There are more than one way of recording the action potential of a nerve. Hodgkin and Huxley used an intracellular microelectrode whose tip was placed inside of the membrane in the immediate neighbourhood of the stimulating electrode with the indifferent electrode situated farther away. The potential changes were observed on the screen of the cathode ray oscilloscope. The beam of electrons which is the recording lever, so to say, is weightless and consequently, it registers all (Fig. 40) changes faithfully and without any time lag. The foregoing figure represent records of the action potential as seen on the oscilloscope screen. The main variation of the

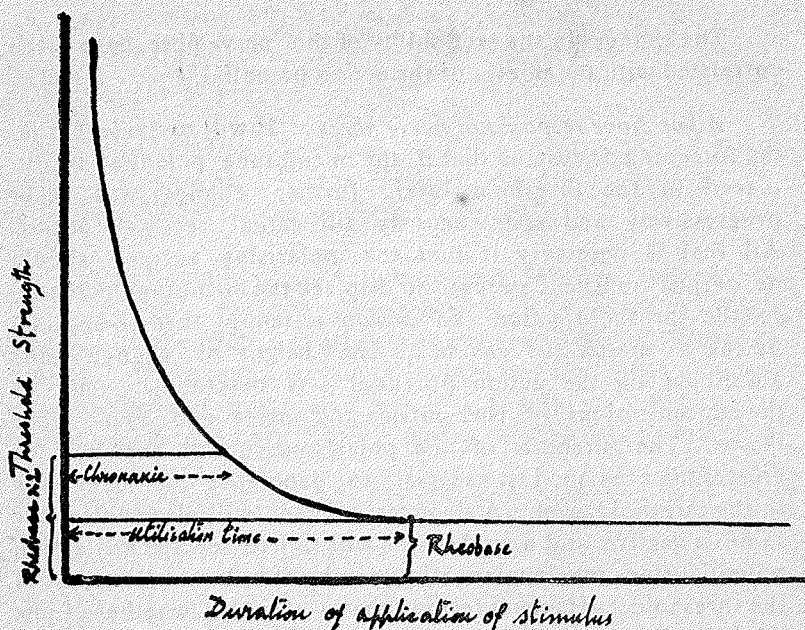


Fig. 41 Strength-duration Curve.

(After Best, C.H. & N.S. Taylor, *Physiological Basis Medical Practice*, 6th ed., Walliam & Wilkins Co., Baltimore)

membrane potential, though conventionally shown in the upward direction, is really (mathematically or algebraically) a reduction of the membrane potential (depolarisation) or a negative variation. Hence, it is consistent to term the first after potential as a negative after potential. The course of the record below the level of the resting potential, on the same grounds, is hence correctly called as a positive after potential.

Nerve cells, muscle fibres and glandular elements are the excitable tissues in the body. By excitability or irritability is meant the ability to respond to an external stimulus. A stimulus itself is defined as a change in the physical or chemical environment of the tissue. Stimuli can be of various kinds :

- 1) Thermal—application of heat or cold ;
- 2) Chemical—mild acids, crystals of salt ;
- 3) Mechanical—pinching the nerve or the

muscle; 4) Electrical. The last named one is the most widely used stimulus in physiological studies. Unlike the other forms of stimuli, electrical stimuli do not injure the tissues and so can be used repetitively. More important than even this, is the facility with which electrical stimuli can be graded in strength which makes it possible to investigate the quantitative aspects of excitability.

It is convenient to discuss at this stage, certain aspects of excitability of a tissue. For a stimulus to be effective, i. e. — to elicit a response from a tissue, it should satisfy certain requirements. It should be of a certain minimum intensity or strength which is known as the threshold value. In addition, it is necessary that this minimum stimulus should be applied for a certain minimum period to the tissue, to evoke a response. There is usually a reciprocal relationship between the stimulus magnitude and the time of application necessary for effective stimulation. Stronger stimuli evoke responses sooner than weaker stimuli. The relationship of these two parameters (stimulus strength and duration of application) has been studied for all excitable tissues. Graphs have been drawn depicting such relationships (Fig. 14). It has been found that for each tissue, there is a minimum stimulus strength whose time of application (utilisation time) is indefinite and such a strength is called the rheobase value. Stimuli of twice the rheobasic value are used and the minimum time of application for these to be effective, is determined. Such a time interval came to be known as the chronaxie which is the duration of application of a stimulus twice the rheobasic strength required to get a response.

Threshold strength has been vaguely defined as the minimum strength of a stimulus to a tissue, necessary to be effective. Such a definition is not satisfactory since the time of application of a stimulus and the rate of rise of the strength of the stimulus also are considerations involved. If the full value of the strength of a stimulus, even though it may be high, is attained very slowly during the time of its application, the stimulus may fail to be effective, for the excitable tissue accommodates itself and becomes unresponsive. Chronaxie is a useful measurement. It has been made use of for comparing the excitability of one tissue with that of another, since it itself is a measure of excitability. Shorter

the chronaxie of a tissue as compared with that of another, more excitable it is. Thus, it has been observed that flexor muscles have shorter chronaxie than extensors; chronaxie of white muscle fibres is shorter than that of red fibres. Plain muscle tissue has longer chronaxie than skeletal or cardiac muscle tissue. Larger calibred nerve fibres have shorter chronaxie than thinner ones. Contrary to expectation, chronaxie of cardiac muscle is actually shortened by vagal stimulation, as also that of intestinal plain muscle. Fatigue lengthens chronaxie.

It was the opinion of Lapique that a skeletal muscle and its motor nerve should have chronaxies of the same order (isochronism), in order for brisk and smooth, muscular contraction to be possible. But strict isochronism is not really necessary. In a

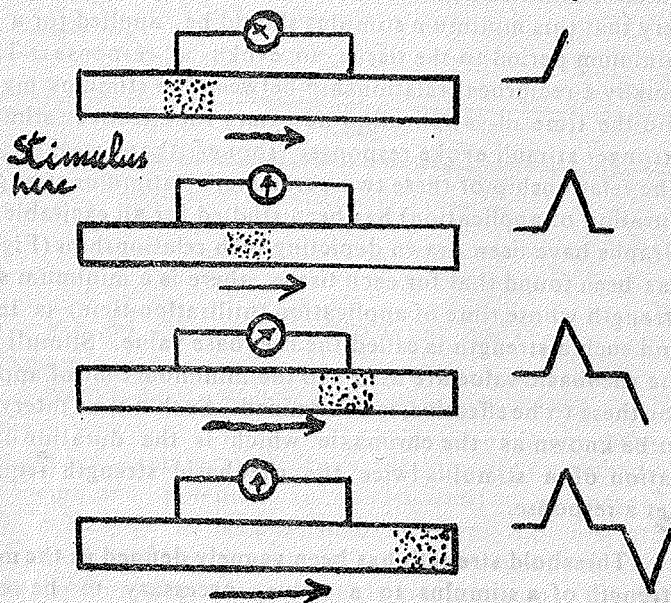


Fig. 42 Biphasic Record

(After Wright, S., Applied Physiology, 11th ed, Oxford Univ. Press, London, 1965)

growing infant, approximate isochronism is established by about the end of the second year of life when all movements become smooth and precise and purposeful.

Modes of recording of an action potential: It is not always necessary or feasible to use intracellular electrodes. Externally placed microelectrodes, wire electrodes and even simple electrodes made of cotton wool drawn into fine points have been used for recording nerve fibre activity.

When two extracellular electrodes are placed sufficiently far apart on a nerve fibre, the record obtained is what has been called a bipolar change. The accompanying figure (Fig. 42) illustrates the sequence of changes in the electrical activity.

It will be seen that, as the impulse travels to the right along the nerve fibre, the patch of negativity comes to lie first under one electrode and then after occupying successive zones in the region between the two electrodes, passes under the second electrode before moving finally to the extreme right. The galvanometer registers the presence of the negative patch under either of the electrodes and thereby the direction and magnitude of current flow is recorded. A biphasic variation indicates a propagated action potential. But this method of recording an action potential is only of historical interest and so is seldom used nowadays. The main defect of this is that it is inconvenient to compare quantitatively, two diphasic records. Hence, monophasic records are obtained by using the same set up as before except that the portion of the nerve fibre (or trunk) under the electrode at the right is crushed so as to render it non-conducting (Fig- 43). Under resting conditions, there is a potential difference between the regions under the electrodes because of the current of injury (crushed part is negative to the intact part of the nerve). Hence, there is a sustained deflection in the galvanometer even while the nerve fibre (trunk) is at rest. As the impulse comes to lie under the first electrode, the existing potential difference is abolished and an upwards sweep of the potential line occurs in the graphic record. When the impulse passes on to the interelectrode region, the potential difference existing while at rest, is reestablished and so the record swings back to the original, level. Since there is only one spike-like

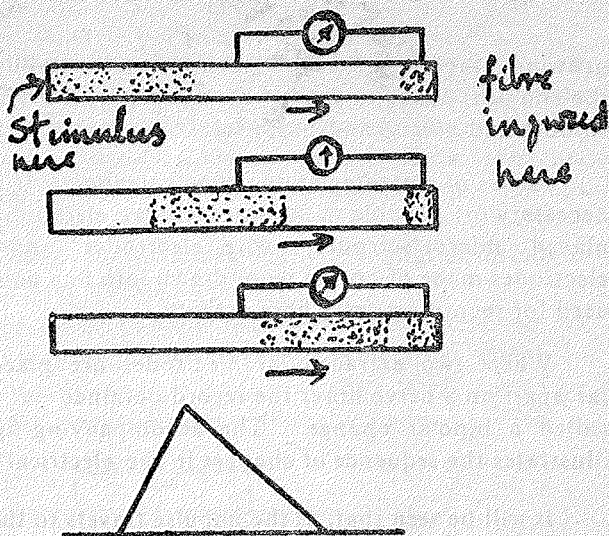


Fig. 43 Monophasic Record

(After Wright, S., Applied Physiology, 11th ed. Oxford Univ. Press, London, 1965)

deflection recorded, this is called a 'spike potential' or a monophasic change. The galvanometer is so connected to the electrodes that the only deflection that occurs is recorded above the base line and not below it. This is convenient as it is easier for the eye to estimate and to actually measure distances above the base line rather than below it (inverted change).

Conduction of an impulse along a nerve fibre :

In the case of a non-myelinated nerve fibre, the mode of conduction is by the formation of local circuits between the zone of activity (patch of negativity) and the adjoining resting region. In the active region, the exterior of the fibre is negative with respect to the immediately adjacent portions of the nerve. A current flow is established from the resting region towards the depolarised zone along the external aspect and from the latter to

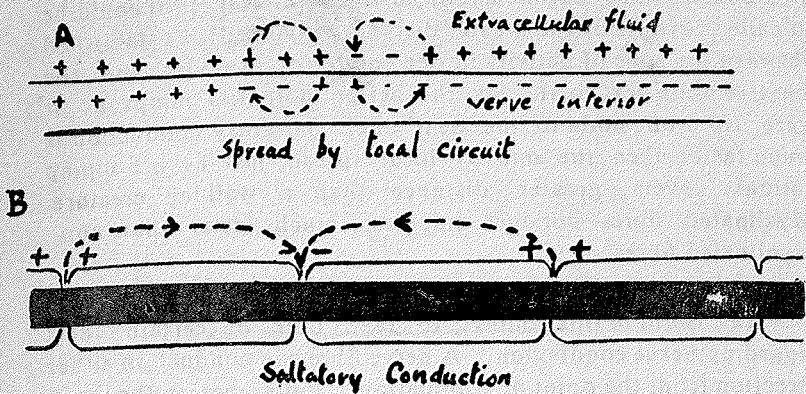


Fig. 44. Conduction of Impulses

the former along the core of the fibre, all this constituting a local circuit. The depolarisation of the resting zone leading on to a reversal of polarity, occurs because of the outward flow of the current in the local circuit and it being of sufficient strength to set up an action potential in what was just an instant before inactive. Another local circuit is now established between the newly active zone and the next adjoining (resting) portion of the nerve. In this manner the impulse (action potential) moves from one spot on the nerve to the next and then to the next and so down the whole length of the nerve fibre. This mode of conduction of an impulse is rather slow, the velocity of conduction not exceeding 1 metre or so per second. Unmyelinated fibres conduct impulses slowly. The term unmyelinated fibre is not strictly accurate since even this has a very thin coating of myelin which because of its thinness however, does not affect the setting up of a local circuit.

In the case of myelinated nerve fibres, conduction is saltatory (saltare – to jump). Huxley and Stampfli explained the basis of this type of spread of an impulse. The heavy coating of myelin in the internodal region, because of its high electrical resistance, precludes the possibility of a local circuit developing. All the same, since the conductivity of the external fluid is very

high compared to that of myelin, a 'local' circuit (if it could be so called because of the greater distance involved) is established between the zone of activity in one node of Ranvier and the inactive node next to it. So, the action potential jumps as it were, from one node to the next one. Saltatory conduction is much faster than the one by local spread, just as a hopping animal covers greater distance than a walking creature. Myelinated fibres conduct impulses much faster than non-myelinated fibres.

It is useful in this context, to take note of certain facts regarding nerve conduction. A nerve fibre can conduct in either direction from the point of stimulation. But nerves in the living body are excited only at one extremity of their courses - at peripheral points (receptors) in sensory fibres and at the spinal level (anterior horn cells) in motor fibres. Thus, 'one way' conduction is a limitation imposed on nerve fibres because of anatomical reasons. Stimulation at an intermediate point in a nerve fibre never occurs in ordinary life. Only under artificial conditions of stimulation in the laboratory, nerve fibres are excited at any point along their lengths. Even among myelinated fibres, those of large calibre conduct faster than those of lesser thickness, because the cores of the former offer freer passage (less resistance) to the flow of currents.

Classification of nerve fibres into different types is made purely in terms of calibre or thickness of the fibres. Different nomenclatures have been employed giving rise to some confusion. One mode of division is based on the elevations in a compound action potential of a nerve trunk composed of fibres both myelinated and nonmyelinated and of varying thicknesses. If the recording electrode is closest to the stimulating electrode, only a single spike may be seen, this resulting from the summed effect of all the potentials of the individual components. But, as the recording electrode is moved away, the individual components, each of which is the composite potential of a particular group of fibres (of the same calibre or of a particular range), are separated out and each elevation is denoted by a letter α , β & γ , etc. Fibres giving rise to the particular elevation is put in the category denoted by the appropriate letter.

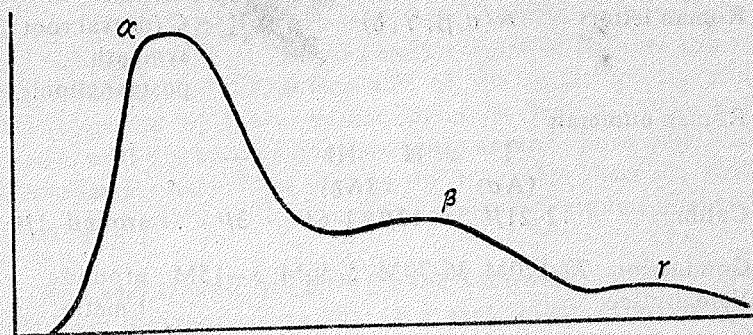


Fig. 45 Compound Action Potential of a nerve trunk

(After Best, C.H. & N.B. Taylor, *The Physiological Basis of Medical Practice*, 8th ed., Williams & Wilkins Co., Baltimore, 1966.)

LLOYD divided myelinated fibres into three categories designated by the Roman numerals I, II & III based on the fibre thicknesses.

group I	—	12 to 21 μ
group II	—	6 to 12 μ
group III	—	1 to 6 μ
group IV	—	nonmyelinated fibres < 1 μ

From the determination of velocities of conduction for myelinated fibres it has been seen that the velocity of conduction is proportional to the calibre, the constant of proportionality being about 6 metres per micron of thickness. For nonmyelinated fibres, velocity is proportional to the square root of the thickness. Since these are around 1 μ in diameter, the speed of conduction is about 1 metre/sec.

There is yet a third categorisation of nerve fibres, on the basis of myelination or otherwise of the nerve fibres. Myelinated fibres are named A and B types and the nonmyelinated ones C.

The following table illustrates the parallelism of the various nomenclatures in this regard :

Roman letters	A ($\alpha, \beta, \gamma, \delta$)			B	C (dorsal root C sympath. postganglionic C)
Roman numerals	I	II	III	—	IV
	(A α)		(A δ)		
Calibre	12-21 μ	6-12 μ	1-6 μ	3 μ	around 1 μ
Conduction Velocity/sec	70-120M	36-70M	5-36M	3-15M	around 1 metre.
Details of action potential			no negative after potential		no negative after potential in the case of spinal dorsal root C fibres only.
Susceptibility to anoxia	high		fairly high		very high for sympathetic postganglionic fibres very little for dorsal root fibre.

The thickest of the myelinated fibres, AI are the afferent fibres of muscle spindles (annulospiral endings) and tendon organs. Motor nerve fibres supplying skeletal muscles are among the largest calibrated fibres. B group fibres form the sympathetic preganglionic fibres arising from the lateral horn cells of the cord (Grey rami Communicantes). Other sensory fibres (A II & A III) innervate touch, pressure and other receptors. The C group fibres are of two kinds - Symp. C are the postganglionic sympathetic fibres forming the white rami communicantes. The others are the fibres subserving pain and temperature sensations.

SYNAPTIC TRANSMISSION

In the beginning of this section it was pointed out that the nervous system, according to Ramon Y Cajal, was made up of innumerable number of independent neurones which exhibited contiguity but not continuity. In any nervous tract or pathway we find regions where one nerve cell (fibre) ends in contact

usually either with a dendron or with the cell body of another neurone. Such regions of contact were termed 'Synapse' by Sherrington. In the case of the anterior horn cell of the spinal cord, it is computed that at least 40% of the surface of the cell body is covered by the end feet (boutons terminaux) of the axons of cells discharging impulses to the anterior horn cells. In some cases, the nerve fibre ending on the next neurone (cell body) may break up into a basket-like network around the cell body.

A typical synapse will have the the following features. The surfaces of the two neurones that face each other at a synapse

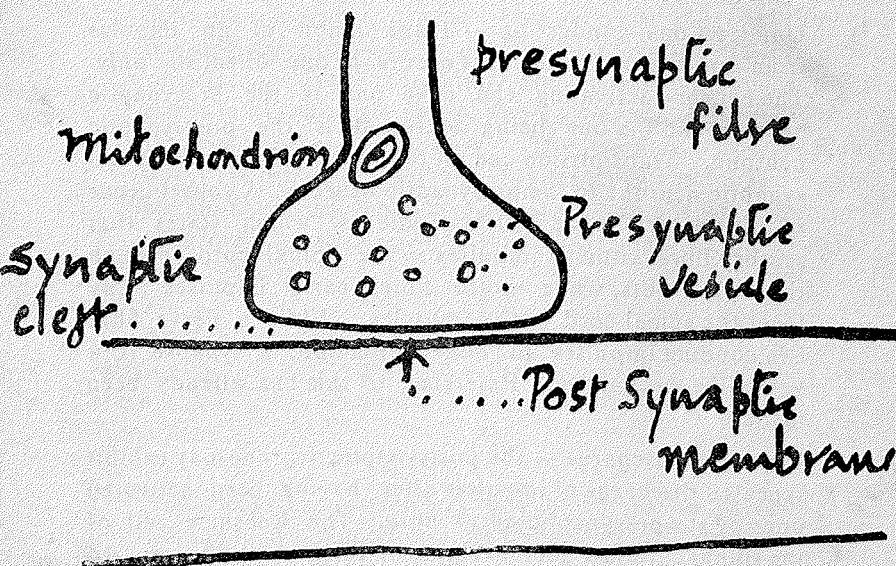


FIG. 46 A SYNAPSE

After Hamilyn, L. H., J. Anat. Lond., 96, 112-120 1962

are called pre-synaptic membrane (first neurone) and post synaptic membrane (second neurone)

1. The presynaptic membrane (of the discharging neurone) is of about $50\text{\AA}$ thickness as revealed by the electron microscope.
2. There is a synaptic space or cleft between the two neurones and it is about $200\text{\AA}$ wide.

3. Electron microscope has revealed the presence of small bag-like structures (synaptic vesicles) in addition to mitochondria in the presynaptic nerve terminal—(300–500A°).
4. The post synaptic membrane shows patches or zones of dense staining.

Conduction from one neurone, across the synapse, to the next neurone is governed by the following principles (properties of synapse).

1. Unidirectional conduction — Transmission of an impulse from one neurone to the next occurs in one direction only. The neurone activating the next one is the presynaptic neurone and the one being activated is the postsynaptic neurone. Transmission cannot take place from the postsynaptic neurone to the presynaptic neurone. A consequence of this property is the Bell-Majendie law which states that sensory fibres conduct impulses to the spinal cord through the dorsal roots, while motor fibres carry impulses away from the spinal cord to the muscles. While a nerve fibre can conduct impulses in either direction, a synapse is a valve-like mechanism. Reference to this has already been made.
2. Repetitive discharge — the postsynaptic neurone may exhibit repeated discharge of impulses after having been activated once by the presynaptic nerve fibre. The Renshaw cell of the spinal cord is a good example of this. Amplification of neuronal activity is the result of this phenomenon.
3. Failure on the part of the post synaptic neurone to transmit, faithfully, the frequency of presynaptic volleys. This is best exemplified in the auditory sensory pathway. While in the auditory nerve fibres the frequency of impulse discharge may be a few hundreds per second, it diminishes at every relay station so that the fibres linking the medial geniculate body with the auditory cortex discharge at a frequency not greater than 70 or thereabouts.
4. Susceptibility to anoxia, ischemia and depressant drugs. The synapse is the weakest link in the nervous system. This is a

built-in safety feature like the fuse in electrical wiring whereby irreversible damage to muscles is avoided.

5. Delay—Synaptic delay of about 0.3–0.6 msec occurs at each synapse.
 - 0.3–0.5 msec — vertebrate mammalian motor neurone (Eccles)
 - 0.5–0.6 msec — at neuromuscular junction.
6. Inhibition — A presynaptic neurone does not excite the postsynaptic neurone in all cases. Inhibition of the postsynaptic neurone occurs frequently. This refers to the abolition of pre-existing activity of the postsynaptic neurone or depression of its excitability. Activation and depression cannot both occur at the same synapse. Some synapses are excitatory in function, others inhibitory. The excitatory presynaptic fibres are different from the inhibitory ones. The same neurone cannot possess excitatory and also inhibitory synapses with the same postsynaptic (Dale's principle) nerve cell.

Mode of Synaptic transmission: The exact mode of transmission across a synapse was the subject of controversy for some years, two possibilities competing with each other for acceptance.

Electrical transmission was thought of as an extension of the mode of conduction of an impulse along a nerve fibre. According to this view, the depolarisation process having reached the presynaptic terminal, set up currents which crossed from the presynaptic fibre into the post synaptic neurone, across the intervening gap. Though this mode of transmission has been seen in invertebrate synapses and also in certain lower vertebrates, it has been ruled out in the case of mammalian synapse, on the undermentioned grounds.

1. It has not been possible to detect currents in the postsynaptic neurone when a depolarising current of sub-threshold strength was passed into the presynaptic nerve fibre.

2. There is a wide disparity in the sizes of the presynaptic and postsynaptic membranes. This precludes, even on theoretical grounds, the activation of the postsynaptic membrane by an electrical spread from the presynaptic terminal. The electrical signals will be weakened considerably so as to become ineffective.
3. The occurrence of a delay during synaptic transmission cannot be accounted for, by an electrical mode of conduction.
4. Inhibition as a synaptic phenomenon, is an insurmountable obstacle for the acceptance of an electrical basis.

It has to be concluded from the evidence presented above, that chemical transmission is the only possibility. Many facts have been gathered in its favour from the experimental work of Dale, Feldberg and co-workers and Katz and others on the neuromuscular synapse. Such investigations have been extended to nerve synapses by Eccles and his associates

All the evidence detailed already as against the electrical mode, is in favour of chemical transmission.

In the last century, Claude Bernard showed the site of action of curare which blocked neuromuscular transmission. Sir Henry Dale, in the beginning of this century, discovered acetyl choline. Dale, Feldberg and others demonstrated that an injection of acetyl choline into the artery supplying a muscle, in an experimental animal, (mammal) evoked a contraction. Katz and others showed that small injections of acetylcholine in curarised frog muscles caused attenuated end plate potentials to be set up. Increasing the concentration of curare, minimised or even abolished such potentials. This has led to the conclusion that acetyl choline is the transmitter in the neuromuscular synapse. In the case of nerve synapses, acetyl choline may be implicated at least in one kind of synapse—that of the collateral branch of a spinal motor neurone axon with the Renshaw cell (Dale's principle). The strong likelihood of its involvement in other synapses is indicated by the presence in nervous tissue of acetylcholine, choline esterase and choline acetylase. Further, the vesicles in the presynaptic terminals revealed by the electron microscope may serve as stores for the transmitter. It has become

possible to demonstrate the occurrence of choline esterase at certain sites in the postsynaptic membrane by histochemical technique of Koelle and Friedenwald. Acetyl choline and choline acetylase have been detected in appreciable amounts in nervous tissue. In a sectioned fibre, choline acetylase is seen to accumulate in the segment continuous with the cell body. It is strongly presumed that acetyl choline is very likely to be a transmitter, at least in some synapses in the nervous system. It has been possible to lay down certain criteria to be satisfied by a substance, in order to qualify to be identified as a transmitter—

1. Its presence in sufficient quantities in the tissue involved.
2. An impulse in the presynaptic fibre should release it in detectable amounts.
3. Introduction of the substance in the synaptic space (electrophoretic injection) should evoke action similar to the natural synaptic action.
4. Pharmacology of the synapse under investigation should be same as that of the suspected transmitter substance, i. e.—the same blocking agents for the synaptic conduction should inactivate or block the action of the substance under investigation. Likewise, in the case of potentiating agents—e.g. eserine or physostigmine in the case of acetyl choline.

Acetyl choline (ach) is a possible transmitter in the central nervous system. It is opined by some that ach and serotonin (5 hydroxy-tryptamine) each act as transmitter at every alternate synapse.

Synaptic transmission involves the following sequence of events:

Impulse in the presynaptic fibre $\longrightarrow$ release of transmitter
 $\longrightarrow$ transmitter action on postsynaptic membrane $\longrightarrow$
 Postsynaptic potential $\longrightarrow$ impulse in postsynaptic neurone.

Post synaptic potential: Recent work with microelectrodes inserted into the muscle fibres (Katz and others) and in the mammalian motor neurones (Eccles and others), has led to the elucidation of the electrical activity at the postsynaptic membrane. In excitatory synapses, the released transmitter acts on

the postsynaptic membrane and depolarises it, setting up an excitatory potential (EPSP). The membrane becomes more permeable to all the ions on the two sides of it, the migration of which along the concentration gradients, results in ionic currents whose direction is indicated in the figure.

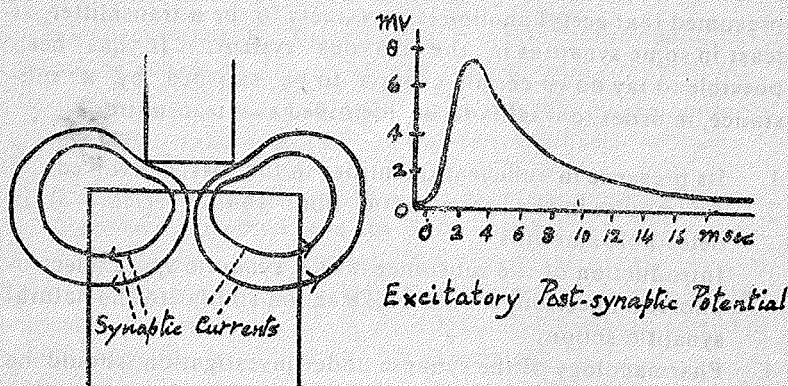


Fig. 47

After Curtiss, D. R. and J. C. Eccles, J. Physiol. (Lond.), 145, 529-546 (1959)

Central Excitatory State: Sherrington, during the course of his monumental work on spinal reflexes, visualised what he called the Central Excitatory State (CES) set up in the cord by afferent impulses reaching it. This decays in less than 20 msec, the effective period occupying the first ten milliseconds or so. During the CES, the motor neurones are hyperexcitable to stimuli. In other words, impulses in an afferent nerve which fail to excite the motoneurones in the absence of CES, are effective during CES. Since the time course of the EPSP is known, it is logical to assume that the CES is manifested as the EPSP both in the magnitude of change and duration. EPSP is the electrical analogue of the CES.

The EPSP once set up and if of sufficient size, will lead on to the generation of an impulse in the subsynaptic neurone. It has been observed that the membrane in the region of the dendrites and the cell body (Soma-dendritic membrane) has a

very high electrical resistance. For the generation of an impulse, local currents will have to flow from the subsynaptic region to the initial segment (I. S.) region of the nerve cell membrane. The figure illustrates this.

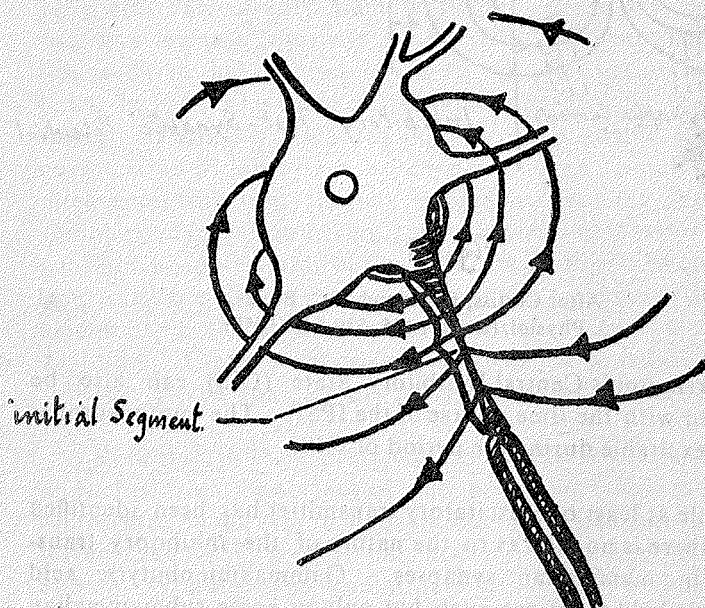


Fig 48 Generation of impulse in a post synaptic neurone.

After Coombs, J. S., D. R. Curtiss and J. C. Eccles,
J. Physiol. (Lond.), 139, 232-349 (1957)

At other synapses, inhibition of the postsynaptic neurone may occur. The action of the transmitter on the post synaptic membrane is to render it permeable to anions only and especially to Cl^- : Consequently, the membrane potential becomes hyperpolarised, as the equilibrium potential for Cl^- is a value on the hyperpolarised side of the resting potential. The time course of the inhibitory post synaptic potential (IPSP) as well as the ionic currents, are represented in fig. 49.

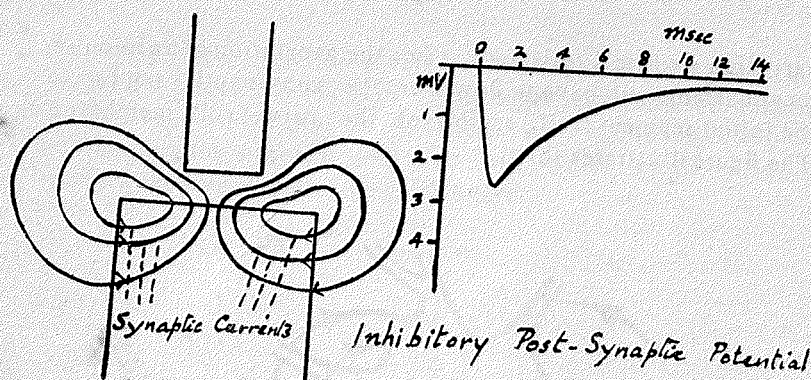


Fig. 49.

After Curtiss, D. R. and J. C. Eccles,
J. Physiol. (Lond.) 145, 529-546 (1959)

Sherrington's Central Inhibitory State (CIS) can also be correlated with the time course of the IPSP. The motoneurons are less excitable during the period of CIS.

While at least one excitatory transmitter has been identified as ach, there is no clue as to the nature of the inhibitory transmitter in mammalian synapses. Gammaaminobutyric acid (GABA) is held to be one such but only in some submammalian animals. It is of some interest to note that the alkaloid, strychnine, is a competitive inhibitor of the unknown inhibitory synaptic transmitter in the manner curare acts in relation to acetylcholine. The toxin elaborated by the bacterium *Botulinum* prevents the release of acetylcholine at sites where it is a transmitter and blocks the excitatory effect of the transmitter on the subsynaptic membrane.

THE PHYSIOLOGY OF THE SENSORY END ORGANS

Information regarding the state of the environment and nature of events occurring in the external world is required by an animal for various purposes like seeking for food, mate and defence against predators. Awareness of one's own body is also necessary in order to perform movements smoothly and purposefully. Pain is preeminently a protective sensation in that it

draws attention to any injury sustained by the animal and evokes responses to avoid further injury.

Sensations are divided into different kinds or *modalities*: touch, warmth, cold, pressure, pain, vision, audition, smell, taste etc. These are the main divisions. There are submodalities, as sweetness, sourness etc. in taste, different tones in audition, different hues in vision and so on. Perception is a process based on basic sensations which are elaborated by the cerebral cortex. It involves a detailed analysis of the stimuli applied and comparison with previous experience of such stimuli and even integration with other closely related sensations. Wetness is a complicated sensation arising from coldness and pressure. Stereognosis is the appreciation of the thickness of objects in addition to length and breadth—in other words, shape and size of the objects held in hand, texture and nature of surfaces touched and such qualities. The pleasantness or otherwise of a sensation is the 'affect' of the tone. Pain is an unpleasant sensation.

Even though there are many cutaneous sensations that can be elicited from the surface of the body, yet each modality is represented on the skin in a punctate or point like manner. Hence, warmth can be experienced only at certain points, cold at others and on. Von Frey and Ruffini were responsible for mapping out touch, cold, warm and even pain spots on the skin.

Receptors: A receptor or *end organ* is a structure which is susceptible to stimulation usually by one form of energy and it sets up an impulse in the afferent nerve fibre or its branch with which it is in contact. More about receptor physiology will be presented later. Sherrington divided receptors into *exteroceptors* and *interoceptors*. The former respond to stimuli originating outside the body and the latter to those arising in the body itself.

Exteroceptors

Vision
Hearing
Smell
Touch
Warmth

Interoceptors

Muscle spindle
Tendon organ
Baroreceptors
Chemoreceptors
Vestibular end organs

Behaviour of receptors: Even though receptors have been classified on the basis of the nature (energy) of a stimulus to which each kind is most susceptible, yet most receptors can be excited by other stimuli though not with the same ease or facility. Comparatively, one form of stimulus (type of energy) is more favoured (has less threshold comparatively) than others by each kind of receptor and it constitutes the 'adequate stimulus'. The eye (light energy—adequate stimulus) provides an excellent example for this generalisation. When a blow is given on the eye itself or in its neighbourhood, or an electric current is passed through the eye, the sensation of a flash of light is caused. Pressure on the eye also elicits such a sensation which is known as a phosphene. Similarly, passage of alternating current into the ear can produce a sensation of sound (sound waves—adequate stimulus for the ear).

Mueller postulated that a receptor however stimulated always gives rise to the same sensation. This fact has been designated Mueller's Law of specific nerve energies. In the last century when this fact was stated, not much was known about sensory processes. It was assumed by Mueller that the nerve activity (later to be identified as an impulse or action potential) varied according to the sensation it gave rise to. The modern enunciation of this well known principle will be that a receptor, in whichever way it is stimulated, evokes the same sensation—the word sensation is used in the place of nerve energy or activity. The impulse generated by a receptor in a nerve fibre does not fundamentally differ from other sensory impulses, as has been found from modern work on nerve physiology. The height of the action potential in a nerve fibre is invariable under a given set of conditions. There cannot be a wide diversity in the shape and size of action potentials in different nerve fibres. The cerebral cortex cannot get a clue as to the nature of the stimulus from the parameters or characteristics of the action potentials set up in the sensory tracts. So, what is the basis of the specificity of a receptor as regards the sensation arising out of its stimulation. The special or heightened susceptibility of a receptor to a particular form of energy, does not seem to depend even on its microscopic structure. For, widely different end organs like Meissner's corpuscle, basket-like nerve endings and even bare nerve terminals (pinna of ear), all subserve touch sensation. The only possible basis for specificity may be the ultramicroscopic

(as yet not revealed under light microscope) details or molecular configuration. Perhaps, it may be that the termination or the final destination of the sensory fibres may be involved in this regard. It has been fancifully remarked that if the visual pathway is connected with the auditory cortex, we may hear light. Likewise, if the auditory pathway is linked to the visual cortex, we may see sound.

Localisation of the points or regions of application of a stimulus is a remarkable property of the sensory nervous system. The area or extent of the skin innervated by a single sensory fibre through its branches is denoted as its receptive field. There is quite a degree of overlap between neighbouring receptive fields. Hence, it may apparently be a paradox that localisation of stimuli of a very accurate degree is possible in the face of such overlap. A sensory unit consist of a sensory nerve fibre and its ramifications. Adrian and Zotterman studied the response patterns—stimulus response curves—in single sensory units and much of the knowledge concerning the coding of information originated from their work. Zotterman has made studies of thermal receptors in particular.

Coding of information in sensory nerve system: While the Morse code employs two signals - a dot and a dash, sensory fibres have to make do with only one—the action potential or impulse of a very short duration of less than a millisecond which can be likened to the dot of the telegraphic code.

1 Modality - this has already been dealt with.

2. Intensity of stimulation - a) Whenever the stimulus strength is increased, the intensity of sensation also increases. For example, if the former rises, say, tenfold, the latter is doubled. That is to say that if the stimulus strength is raised from one unit to ten units, the sensation magnitude rises by only one unit. If the stimulus is increased a hundred fold, sensation is increased tenfold. Thus, there seems to be a constant proportion, ($\frac{1}{10}$) between the rise in the sensation and that of the stimulus over moderate stimulus ranges. The ratio between the two—the Weber fraction—is constant. The frequency of impulse discharge rises with the intensity of the stimulus. There is, at least over the

range of medium stimulus strengths, a linear relationship (direct proportion) between the frequency of impulse discharge and the logarithm of the stimulus strength. This relationship is mathematically expressed as the Weber-Fechner Law.

$$S = K \log \frac{I}{I_0} \text{ wherein } S = \text{Sensation magnitude}$$

$I = \text{Intensity of a given stimulus}$
 $I_0 = \text{Intensity of threshold stimulus}$
 $K = \text{Constant of proportionality}$

This law is obeyed only for moderate intensities of stimulation. The cerebral cortex translates the rate of impulse production from the receptor, into intensity of sensation. This mode of transmitting information regarding intensity, holds good for receptors which adapt slowly (see below).

b) In regard of rapidly adapting receptors, frequency of impulse discharge cannot be a means of conveying information pertaining to the strength of stimulus. A stronger stimulus will excite more receptors than a weaker one. The sensory cortex correlates intensity of stimulus with the number of activated receptors in such a case.

3. Duration of stimulation :— Not all receptors continue to be active when stimulation is prolonged. Some receptors discharge an impulse or two at the commencement of stimulation and then become silent. These are said to adapt very rapidly. Touch receptors belong to this category. It is on account of this, a subject ceases to be aware of the clothes on his body a short time after he puts them on. Rapid adaptation releases the sensory cortex for reception of other stimuli. Cristae of semicircular canals also belong to this category. A large variety of receptors adapt rather more slowly — retina, hair cells of Corti, and thermal receptors. Still slower in adaptation are some of the proprioceptors like the muscle spindle, and maculae in inner ear. Pain receptors can be considered to be almost non-adapting.

Adaptation to stimulation is not to be confused with fatigue. A receptor which has adapted to one stimulus is ready to be

excited by another of the same kind. But not so during fatigue when a fresh stimulus fails to evoke a response. Further, the rate of adaptation is not dependent on intensity of stimulation whereas fatigue appears sooner with stronger stimulation.

Receptor Potential: A link in the sequence of events leading on to the excitation of a receptor is the generation of a receptor potential. A stimulus depolarises the sensory nerve terminal arising from a receptor. It has been possible to study the characteristics of the receptor potential in a Pacinian corpuscle and in muscle spindles of lower animals. The quantitative studies of Gray and others have yielded several facts regarding the receptor potential. Generator potential is an alternative term used, though a distinction is sometimes made between the two. The receptor potential (like EPSP) is a graded phenomenon, not capable of spreading (propagation) and receptor potentials can be summated. How a stimulus brings about such a change in potential, is not yet elucidated. In the case of a few receptors, it is possible that a chemical transmitter may be implicated. When a receptor potential attains threshold magnitude, an impulse may be fired from the receptor. Even repetitive discharge may occur if the receptor potential persists at the threshold level.

The sensory system of the brain analyses the information obtained from the receptors in three ways and utilises the results of the analysis for initiation and regulation of movements as well as for purely vegetative functions of the body.

a) *Localisation of stimulus:* All cutaneous stimuli are localised i.e. the point of stimulation on the body surface is identified with varying accuracy depending on the part of the body involved. The anatomical basis for this is the division of the body surface into dermatomes, each of which is innervated by a sensory spinal root. Dermatomes for all dorsal spinal roots as well as for the cranial nerves (V nerve) have been mapped out by several workers. It is necessary to section at least three roots above and three below the one whose distribution has to be worked out. Neighbouring dermatomes show overlap at the margins. Also the extent of a dermatome for one modality may not be the same as for another.

Discrimination : Intensity discrimination is based on impulse discharge and the number of receptors activated. Spatial discrimination—tactile or two-point discrimination—is a faculty attributed to the sensory cortex. In spite of the overlap of receptive fields of two neighbouring sensory nerve fibres, it is remarkable that accurate localisation and spatial discrimination is possible. The clues which lead to such processes arise from the receptors which are maximally stimulated. If activity is set up in two closely placed sensory fibres, the one with the greater frequency of impulses inhibits the activity of the other one. Where receptive fields overlap, the receptors, in the region of overlap are, so to say, silenced. This is termed as *Mutual Inhibition*. Since these receptors are in the periphery of the receptive field, such an inhibition is also termed *Lateral Inhibition*. The sensory cortex is not evolved to directly recognise centres of activity in a receptive field, but only boundaries or perimeters of such activity.

Integration of sensations : This term refers to the processes by means of which new sensations are compared with past ones and are interpreted in the light of previous experiences. Memories of more recent sensations are piled up on those gone before, for future reference.

Wakeful state : The discovery of the reticular system has helped in the understanding of mechanisms underlying the wakeful state. All the sensory pathways give off collaterals which go to form the ascending reticular activating system (ARAS). The constant excitation of the various receptors results in a continuous barrage of impulses travelling up the ARAS and bombarding the whole of the cerebral grey mantle. As a result, reverberating circuits are set up between the cortex and thalamus. Thus, sensory impulses are said to maintain the wakeful state.

THE CUTANEOUS SENSATIONS

The sensations that can be evoked by the stimulation of receptors in the skin are those of touch, warmth, cold and pain. The problem of pain is discussed separately and at fair length, in view of its clinical importance.

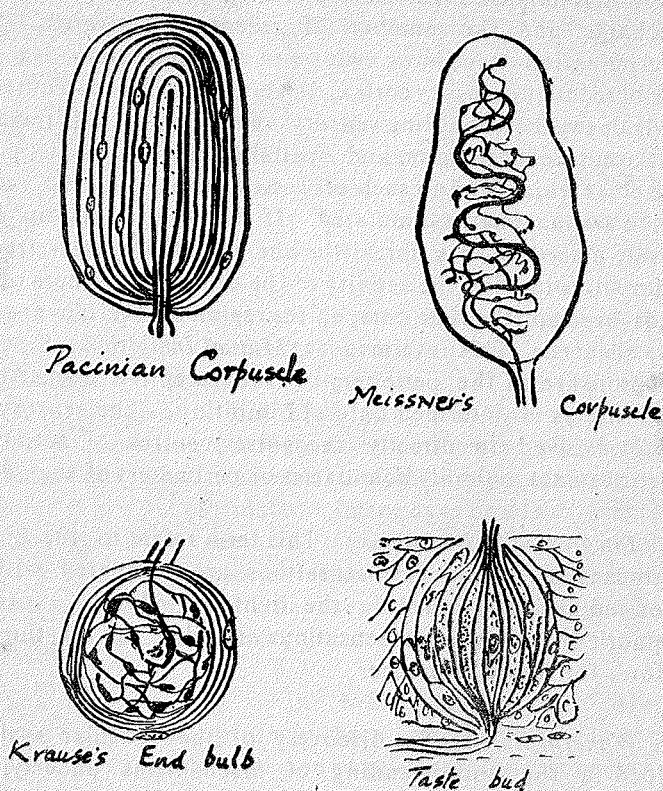


Fig. 50.

Touch sensation is caused by the excitation of skin receptors like the Meissner's corpuscles in the dermal papillae (finger tip), basket-like nerve endings around hair follicles, Merkel's discs (in glabrous skin as on the lips and the glans penis) and even unencapsulated nerve endings, as in the lobe of the ear. It is remarkable that a wide variety (structurally) of receptors subserve the same sensation. This fact has made certain workers even question the validity Mueller's law, which nevertheless can be defended convincingly (see under receptor specificity). The afferent fibres carrying impulses from the touch receptors are myelinated (fine and medium calibre) and their cells of origin are found in the posterior root ganglia. The spinal tracts

responsible for conveying information from these receptors, are the ventral spinothalamic tract and the posterior columns (see under tracts).

Deformation of the skin, as caused by pressure applied to a small area, even almost a 'point', while the surrounding skin is not affected, is what gives rise to the sense of touch. Von Frey Ruffini and others have shown that there are special spots on the skin which are specialised for touch (touch spots). Light touch is evoked when the skin is lightly touched, either with a wisp of cotton wool or even with the end of a hair, as in the case of the Von Frey's hair aesthesiometer. A logical corollary to light touch, is the accuracy with which the point on the skin which is stimulated, is located by the brain. This localisation is based on the dermatomal organisation of the body surface. A few touch receptors are excited even when seemingly a very small area is touched. On theoretical grounds, it appears that it is the receptors which are excited to the greatest degree, that give a clue to the exact site touched. The process underlying localisation in the case of touch, is somewhat ill understood since the touch receptor adapts rapidly. The receptor discharges at the most one or two impulses when excited and becomes silent thereafter. The usual explanation, as in the case of nonadapting or slowly adapting receptors, cannot be as such extended to the touch receptors. But similar mechanisms must be responsible even in the case of momentary touch, unlike for steady light pressure, where mechanisms characteristic of slowly adapting receptors, can hold good. Tactile localisation is very accurate at the finger tips, tip of the nose and the region around the mouth and in general, over the whole of the face. It is also well developed on the dorsal aspect of the hand. It is very poor over the soles of feet, and the gluteal region. Other areas are intermediate, as far as this faculty is concerned.

Tactile discrimination : Allied to the above mentioned function, is the ability to distinguish between two tactile stimuli, even when they are simultaneously applied to the skin at points very close to each other. When this discrimination is of a high degree, the two stimuli can be felt separately, even though the distance between the points touched is very small, even a few millimetres. Wherever tactile localisation is accurate, this two-point sensibility

is also of the highest degree. Similarly, wherever the former is of a low degree so also is the latter. This property of the nervous system is tested by a compass aesthesiometer.

It has been held that mere awareness of a touch stimulus (general touch, as the anatomists call it) arises out of the coursing of 'touch' impulses along the ventral spinothalamic can thus be put tract and that the posterior columns are responsible for tactile localisation (special touch) and discrimination. In view of the revision of ideas regarding the working of sensory systems in the brain, it is highly doubtful whether such ideas can be valid. Both tracts must be simultaneously involved in all the aspects of touch - awareness, localisation and discrimination. Only Lesions of central pathways or the sensory cortex leave the awareness intact without localisation.

It is useful to emphasize the fact that touch is the most rapidly 'adapting' of the sensations. This is evident from the fact that we cease to be aware of our clothes, soon after we put them on. But whenever we move our limbs or change our posture, we are aware of our clothes.

Light pressure cannot be divorced from touch. It differs from touch in that the time of application of the stimulus is somewhat longer and the pressure or force may be somewhat greater. The modern trend is to call both by one name, as touch-pressure.

Vibration sensibility - This refers to the perception of a temporal (spread over some time interval) pattern of pressure stimuli, repeated at a rapid rate. Though it is felt best over bony prominences, when the stem of a vibrating tuning fork is placed on them, it is not an osseous sensation.

Warm and Cold sensations: There are two types of receptors—one discharges impulses more and more rapidly with a rise in temperature (warmth or Ruffini's receptor) and the other, with a fall in temperature (cold receptor or Krause's end bulb). Even bare nerve endings may take the role of these receptors. Cold receptors give a tonic (sustained) discharge, while the warmth receptors give a spluttering (of rapidly varying frequency) type of discharge. It is very probable that these receptors.

signal changes in the velocity of biochemical reactions. Warmth receptors are situated deeper under the skin than the cold end organs, though both are seen at the base of dermal papillae. The minimum changes in temperature, effective in exciting these receptors, are a rise in temperature of $0.001^{\circ}\text{C/sec.}$ for a warmth receptor and a fall of $0.004^{\circ}\text{C/sec.}$ for the cold receptor. Like touch spots, there are warm and cold spots (less in number than touch or pain spots) both being separate and not coincident. Changes in environmental temperature or even that of blood flowing under the skin, can be effective in stimulating these receptors.

Wooden objects feel relatively warmer than metal objects, since the former are non-conductors of heat and do not carry heat away from the hand holding or touching them. Metal articles conduct heat from the hand and thereby cause a fall in temperature of the skin. This is the reason for their 'coldness'.

Persistent cold sensation is that which results when a cold object is pressed on the skin, especially on the forehead momentarily and then taken off. The cold sensation continues even though the skin is warming up after the object has been removed. This may be due to a steady discharge from the cold receptor. Again, some objects at temperatures round about 45°C , feel cold when touched. All temperatures below 38°C or so, can evoke a cold sensation. The ranges of temperatures within which the cold and warm receptors are active, overlap to some extent and this is between a little over 20°C and upto about 38°C . The cold receptor is excited more and more at temperatures above 45°C , at which range the warmth receptor is silent. At temperatures above 45°C , a sensation of cold may occur and this is known as paradoxical cold sensation. Menthol and such counter irritants, externally applied, alter the threshold of cold receptors and thereby bring about their stimulation. That is why there is a sensation of 'coolness'.

The nerve fibres subserving warmth sensation are nonmyelinated C type, making contacts with the lateral spinothalamic tract. Cold fibres are thickly myelinated. The central mechanisms underlying the perception of warmth and cold, are obscure.

A very remarkable thermal receptor is the pit organ of certain vipers of the new world. This structure can help the snake to detect warm blooded animals in its surroundings, even in the dark. The infra red radiations emanating from the bodies of the small mammals, enable the reptile to prey on them.

Itch and tickle: The phenomenon of itching is the result of a lowering of the threshold of pain fibres. This is proved by the fact that when the lateral spinothalamic tract is divided, itch is abolished, as also shown by the failure of a histamine injection to produce itching. Scratching, to the point of producing pain or smarting in a neighbouring area or even at the site of itching, makes the itch disappear. Antipruritic agents neutralise the action of histamine. Itching is usually produced by certain substances and by the stings of insects like the bed bug and the mosquito. Even a protein splitting enzyme may be responsible for producing itch.

Tickle is a compound sensation having two elements, touch and pain. Tickle is produced by stroking or touching sensitive areas like the arm pit, sides of the trunk, facial region round the mouth etc. Interference with touch or pain fibres will make tickle disappear. The susceptibility to tickling stimuli varies widely among people. Psychological factors and previous exposure to stimuli influence it.

THE PROPERTIES OF SPINAL REFLEXES

Sherrington was a pioneer in neurophysiological studies. His monumental work on spinal reflexes laid a solid foundation for subsequent advances in this field.

A spinal reflex arc consists of the following elements:

- a. A receptor which, when excited, discharges impulses into—(b)
- b. The afferent nerve fibre—the peripheral process of the neurone in the dorsal root ganglion, and its central process making contact with the spinal motor neurone.

- c. The synaptic region (the region of contact between the afferent fibre and the spinal motor neurone) and the cell body of the motor neurone forming the spinal reflex centre.
- d. The efferent limb or the axon of the motor neurone.
- e. The effector organ — skeletal muscle.

Reflexes need not always result in muscle contraction. Secretory activity as in a gland may occur or even plain muscle may exhibit contractions. These constitute secretory and visceral reflexes.

Reflexes can be divided into monosynaptic and polysynaptic reflexes according as the reflex arc includes one synapse or more than one synapse. Division of reflexes into extensor or flexor reflexes is another physiological convention. Clinically, reflexes fall into three categories of superficial, deep and visceral or organic reflexes.

Properties of reflex arc : Since synapses feature in the reflex arc, all the properties of a synapse are exhibited by a spinal reflex. In addition, the undermentioned ones have been shown to be properties of the spinal reflexes. The properties, numbered 1-9 can be easily demonstrated in a flexor reflex.

1. **Localisation :** A given stimulus will always elicit the same specific effect, no matter however many times, one repeats the stimulus. Thus, a painful or noxious stimulus to the foot pad will always bring about the withdrawal of the limb. In other words, the main pathway of the reflex is invariable. The same spinal segments or motor neurones are involved each time as far as the main effect of the reflex is concerned.

2. **Co-ordination :** When a particular muscle is excited as the result of a reflex action, its contraction will bring about a purposeful and smooth movement of a joint or joints or a whole limb. This is possible because the synergists of the excited muscle are also activated and so a well-coordinated movement results.

3. **Reciprocal innervation :** In a reflex wherein a withdrawal of a limb occurs as a result of flexor action, the extensors of the limb are made to relax in order not to oppose the flexor action

and thereby avoid resistance to the flexion movement. Thus, whenever any group of muscles is excited, the antagonists are inhibited at the same time.

4. Delay: A certain irreducible period of time elapses between the instant of application of a stimulus and the onset of the reflex effect. This period is the total reflex delay and is composed of the following intervals — a) Time of conduction of the nerve impulse from the receptor to the spinal centre along the afferent limb of the reflex arc. b) Synaptic delay at the reflex centre. Least delay will be in a monosynaptic reflex and it is less than a millisecond. It is longer if the number of synapses is greater than one. Synaptic delay at the reflex centre is also referred to as 'central reflex time'. A flexor reflex will have much longer central reflex time as it is a multi or polysynaptic reflex. c) The conduction time in the efferent limb.

5. Summation: If, when an afferent nerve is stimulated with a stimulus of certain strength there is no reflex effect produced, with repetition of the same stimulus with very little interval in between the stimuli, a summation of the reflex 'effects' occurs and a visible or recordable reflex effect occurs. Such a summation is known as *Temporal Summation* (pertaining to time). On the other hand, if two afferent nerve trunks are excited together, a reflex effect might result (spatial summation), while stimulation of each trunk alone may not be effective. The reflex effects due to the excitation of the two nerve trunks are said to be spatially summated. In the former case — temporal summation — the excitatory state set up in the reflex centre by a first volley of impulses arriving along the afferent nerve is added on to that arising out of a second volley and the summed effect may produce a reflex response. According to Sherrington, a central excitatory state is set up by a single volley at the reflex centre and this lasts for some time within which the facilitation of the effect of a second volley, if set up, will occur. This period was called as the Central Excitatory State (CES). The central excitatory state has now been correlated with the duration of the excitatory postsynaptic potential (EPSP) — Temporal summation does not seem to occur under natural conditions. However, this can be demonstrated under experimental conditions. Spatial summations does seem to be a feature of reflex facilitation. It is

called so because the effect of the excitation of an area on the body surface which is innervated by an afferent nerve is added on to that caused by the stimulation of a neighbouring skin area innervated by another nerve — the effects of two areas (spatial) excited together are summated.

6. **Fractionation:** All the motor neurones in the cord that innervate a given muscle constitute together 'the motor neurone pool' for the particular muscle. Stimulation of any afferent nerve trunk causes only a few of the neurones of the motoneurone pool to fire impulses. This can be demonstrated by comparing tensions developed in the muscle when stimulated directly through its motor nerve and reflexly through one afferent nerve trunk. The former is much greater than the latter. An afferent nerve trunk commands or brings about the activity of only a fraction or some of the neurones only of a motoneurone pool.

7. **Convergence:** This is a consequence of fractionation. Since many afferent nerves connect with a motoneurone pool, it follows that they all converge on to the same group of motoneurones. When each of the afferent trunks is stimulated separately and the reflex tensions produced are summed up, the total will be more than the tension set up by the stimulation of the motor nerve itself.

8. **Occlusion:** This is also a phenomenon related to fractionation. While each afferent nerve commands a few of the motor neurones of the pool, it will also share some of these neurones with another afferent nerve. If two afferent nerves are stimulated one after the other and the resulting tensions are added, the total will be more than if the two nerves are excited together. This is so because the motor neurones shared by the two nerves will be excited only once when both nerves are stimulated together.

9. **Subliminal fringe:** When strong stimuli are applied simultaneously to two afferent nerves, occlusion occurs, as described above. When a weak stimulus is used on two afferent nerves at first together and later separately, it is found that joint stimulation produces a greater tension than the sum of the effects

of separate stimulation, contrary to what occurs with occlusion. When a weak stimulus is employed, while the cells in the effective excitatory field are made to discharge, cells in a narrow zone (fringe) surrounding the excited neurones will be activated only to a subthreshold level. If another nerve is stimulated at the same time, cells in the subthreshold zone will be further stimulated so as to actually discharge impulses. Such cells are said to be in the subliminal fringe, excitation of which will be due to facilitation caused by the simultaneous activation of more than one afferent nerve which share the cells in the subliminal fringe.

The undermentioned properties can be demonstrated in extensor reflexes: e.g. extension of a limb when pressure is applied to a foot pad.

10. Inhibition: The suppression (inhibition) of the activity of a nerve cell, eg.—the spinal motor neurone, is necessary sometimes in order to prevent prolongation of a response in a spinal reflex; to inhibit the action of the antagonists to a muscle or a group of muscles which are involved in a reflex, the effect of which is therefore not involved in a reflex the effect of which is therefore not impeded or restrained; also to avoid or abolish the activity of nerve cells lying not on the reflex pathways and whose action is extraneous and not pertinent to the desired or expected reflex effect. Three different modes of inhibition have been described.

Firstly, in a monosynaptic reflex, best exemplified by the myotatic or stretch reflex, the simultaneous (or even commencing in advance of the stretch stimulus) excitation of a cutaneous afferent nerve will suppress the stretch reflex. The pathway of the inhibitory reflex in this mechanism is made up of at least three neuronal links. In this kind of inhibition an inhibitory transmitter is released by an interneurone at its synapses with the motor neurone (anterior horn cell) and thereby produces an inhibitory postsynaptic potential which causes a hyperpolarisation of the subsynaptic membrane, which state precludes the possibility of its excitation for a certain duration of time. This period was originally termed as the Central Inhibitory State (CIS), by Sherrington. The inhibitory post-synaptic potential, both in its time course and magnitude, is the electrical manifestation of the

CIS. Direct or post-synaptic inhibition is the name given to this variety of inhibition. Such an inhibition occurs also when a muscle is over-stretched. This is seen in the so called lengthening reaction (see elsewhere). In this case, the excess degree of stretching of a muscle excites the Golgi organs in its own tendon which in turn bring about the inhibition of the motor neurones of the same muscle.

The chemical nature of the inhibitory transmitter is yet a matter of mystery. Gammaamino-butyric acid (GABA) is an inhibitory transmitter whose presence has been revealed at least in inhibitory synapses of the lower orders of animals.

A second mode of inhibition is by an action on the presynaptic nerve fibre preventing the release of the excitatory transmitter and this brings about inhibition (actually an absence of excitation) of the anterior horn cell (motoneurone). In an extensor reflex, stimulation of any afferent nerve will bring about such a presynaptic inhibition of the extensor reflex.

A third kind of inhibition is what is seen at the synapse between the Renshaw cell (see below) and the spinal motoneurone, preventing the activity of the motoneurone. Natural or experimental excitation of the motor axons, will inhibit the motoneurone activity indirectly. Collateral branches of the motor axons release acetylcholine at their junctions with Renshaw cells present in the neighbourhood of the motoneurones. The former in their turn connect up with the latter by short axons through which an inhibitory effect is exerted on the motoneurones. Whether this third form of inhibition is really different from direct or post-synaptic inhibition and merits to be put under a separate category, is not known. The purpose of Renshaw cell inhibition seems to be to stabilise the impulse discharge frequency of the anterior horn cell.

11. Rebound: When a reflex has been suppressed, as in the case of the postsynaptic inhibition, it will reappear with greater force as soon as the inhibition is withdrawn. The latent period (0.2 second) between the cessation of inhibition and onset of rebound is longer than for the original reflex effect in the absence of inhibition. The phenomenon of clonus seen in upper

motor neurone lesions is due to alternating inhibition and rebound. The mechanism underlying rebound has not been elucidated.

12. Successive induction: A reflex, after it has run its course, facilitates another which follows it immediately. When the two reflexes are of the same type, such action is called positive successive induction. According to Sherrington, a parasite crawling on the skin gives rise to a scratch reflex which shows positive induction. That is why the hopping movement was said to have been evolved by the flea to evade the scratch reflex.

It is somewhat difficult to clearly distinguish between rebound and negative successive induction. Two antagonistic reflexes facilitate each other so that one can alternate with the other. This is due to negative successive induction. Rebound occurs when a reflex is just inhibited without setting up an opposing reflex, while in negative induction, antagonistic reflexes facilitate each other. Alternate extension and flexion of the limb occur rhythmically in walking, which needs no conscious effort and is automatic. Jaw movements, as in mastication, also fall under this category. De-afferentation (sectioning posterior roots) of the muscles does not affect such movements, suggesting that central mechanisms are involved in successive induction. Rebound may be responsible along with negative induction for acts like walking and biting.

13. Recruitment: This is seen in an extensor reflex. The full effect or vigour of a flexor reflex comes on almost instantaneously or explosively. But the effect of an extensor reflex is increased gradually with motor units being activated in larger and larger numbers. The stimulus strength required to evoke recruitment remains constant throughout the duration of the reflex. Decerebrate animals show this property, while a spinal animal is not suitable for this purpose. Recruitment of more and more motor units may result even from after discharge. After the passage of the impulses through the main reflex (shortest) pathway, other nerve impulses continue to traverse through alternative or collateral routes to excite more neurones. An extensor reflex is slow in onset, builds up to a maximum gradually and also wanes off slowly. A flexor reflex is quick in onset, appears explosi-

vely and stops suddenly. Sherrington called the flexor reflex as a d'emblee reflex. Respiratory muscles on the other hand, show recruitment—as in inspiration.

14 After discharge: In a flexor reflex, the response lasts for a very short period and no after effect ensues, or if at all it does, it is very brief. In extensor reflexes, the main effect is continued by the reflex centre discharging impulses to prolong the activity of the muscles. Stronger stimuli increase the duration of the after discharge, which Sherrington considered to be analagous to the momentum of bodies in motion. After discharge may bring about clonic or even tetanic contractions. The routing of the afferent impulses through longer and longer chains of internuncial neurones before arriving at the reflex centre is the basis of after discharge. Proprioceptive impulses originating in the active muscles are not responsible for after discharge since de-afferentation of these does not abolish after discharge.

15. Fatigue: A reflex effect becomes weaker with repetition. Fatigue cannot be attributed to nerve fibres. It implicates the spinal neurones themselves. The synapses are the weakest links in the reflex arcs and they are very vulnerable to the effects of repetitive stimuli.

16. Block or resistance. Only one way conduction of impulses is possible in a reflex arc, synapses rendering it impossible for conduction in the reverse direction. Block to the passage of an impulse even in the normal direction may occur owing to the inhibition at synapses. Strychnine is a drug which abolishes such a block so that an impulse set up in any afferent pathway can spread in diverse pathways to excite a very large number of motor units widely distributed. Convulsions will result from this.

THE PATHWAYS IN THE SPINAL CORD

The grey matter of the spinal cord consists of five well-recognized groups of nerve cells. In the anterior horn, the multipolar anterior horn (motor) cells are seen forming the chief motor nucleus of the cord. At the base of the posterior horn,

near the central canal, there is another collection of cells known as Clark's column (dorsal nucleus—Ranson and Clark). Midway between the posterior and anterior column, causing an elevation of the lateral surface of the grey matter and confined to the thoracic and upper lumbar segments, are the so called lateral horn cells which give rise to preganglionic fibres of the sympathetic nervous system. In the substance of the posterior horn extending from its base to the tip of the horn, are distributed the small cells forming the chief sensory nucleus of the spinal cord. Capping the posterior horn is a mass of gelatinous material containing cells and going by the name *Substantia Gelatinosa Rolando*. These relay some of the primary sensory fibres whose cell bodies are in the dorsal root ganglia. The cells of the dorsal root ganglia constitute the primary neurones for all ascending pathways. Lateral to the base of the posterior horn, is a fine network of filaments, some belonging to the cells of the grey matter of the cord and constituting the reticular formation of the cord in the cervical region where it is prominent.

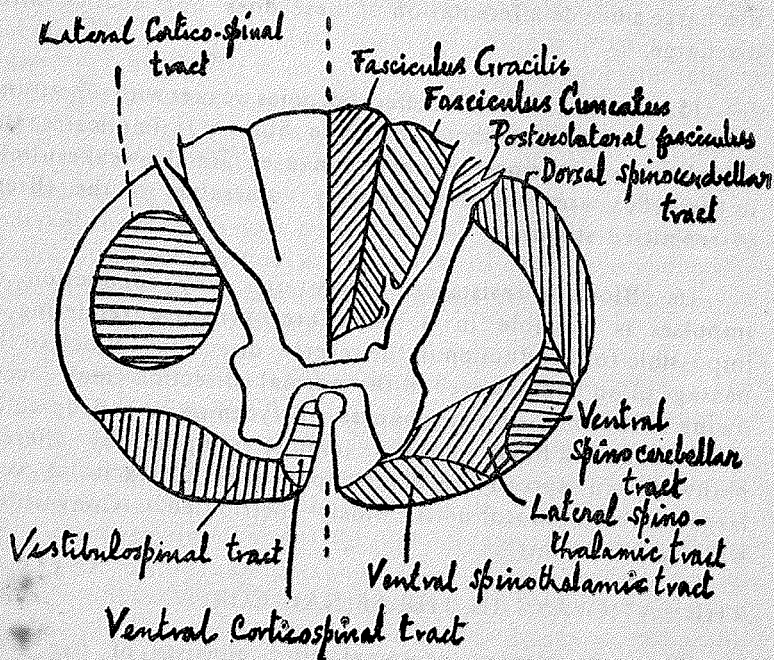


Fig. 51. The Spinal Tracts

From Mettler, Fred A.: Neuroanatomy, St. Louis, 1948,
The C. V. Mosby Co.

Spinal tracts : These are of 3 kinds.

a) ascending b) descending c) intersegmental.

Ascending tracts : The chief sensory tracts are the Spinothalamic tracts the Fasciculus Cuneatus and the Fasciculus Gracilis

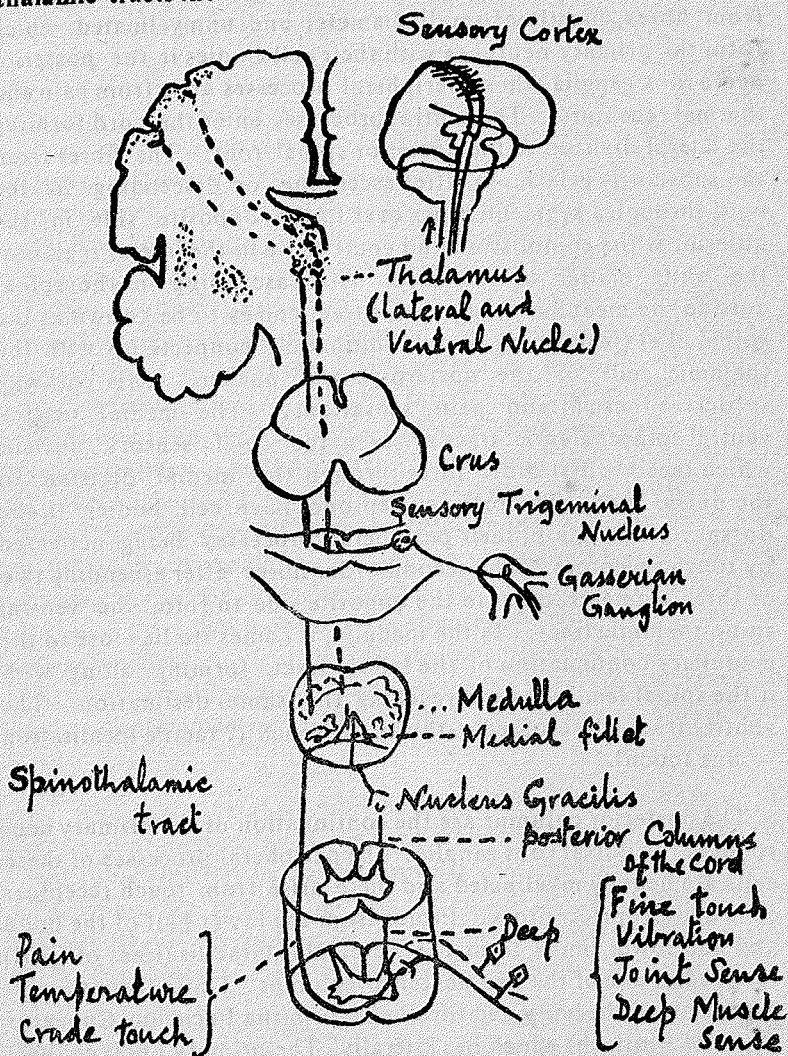


Fig. 52. The Sensory Pathways

From Warner, E. C., Savilles System of Clinical Medicine, XIV ed.
Orient Longmans Ltd., P. 1048 - by courtesy of Edward Arnold
(Publishers) Ltd. London.

(posterior columns). The spino-thalamic tracts are two in number, the lateral of the two is formed by the fibres arising in the substantia gelatinosa. These cells themselves receive impulses from fibres, mostly of small diameter and unmyelinated, which form the primary neurones with their cell bodies in the posterior nerve root ganglia whose peripheral processes arise from pain and thermal receptors. The central processes enter the cord forming the lateral division of the posterior spinal root. The fibres from the substantia gelatinosa, after ascending or descending in the cord through a segment, cross over to the opposite side in the anterior white commissure and come to lie in the lateral region of the white matter of the cord. After ascending in the spinal cord to the medullary region, this tract comes to be known as the spinal fillet (lemniscus) and it ultimately connects up with the thalamic cells of the postero-ventral nucleus. This pathway subserves thermal and pain sensations. The medial or the ventral spinothalamic tract arises in the chief sensory nucleus which receives first order fibres through the medial division of the dorsal root. The primary neurones have cell bodies in the dorsal root ganglion, their peripheral processes being activated by touch receptors. The second order fibres after ascending two or three segments, cross to the opposite side to form the ventral spino-thalamic tract. In the medulla, it comes to lie close to the medullary continuation of the lateral tract, forming along with it the spinal lemniscus and reaching the same destination. The ventral tract is a crossed pathway for touch (? tactile localisation — fine touch).

The posterior columns are the continuation of the primary neurones in the dorsal root ganglia. The peripheral processes of these cells are heavily myelinated and these arise from touch receptors cells and proprioceptors. Fibres from the lower half of the body and the lower limbs form the Fasciculus Gracilis (tract of Goll) the medial one of the two posterior columns. Those from the upper parts of the body and forelimbs form the Fasciculus Cuneatus (tract of Burdach) which lies laterally. The primary fibres connect up with nucleus Gracilis and nucleus Cuneatus in the medulla. Fresh fibres arise from these nuclei and immediately cross over to the opposite side forming the sensory decussation of the medulla. Subsequently they ascend in the medial fillet to end in the postero-

ventral nucleus of the thalamus. The two dorsal columns of the cord and their medullary extensions subserve touch (tactile localisation and tactile discrimination.), vibration sense and sense of position and movement and conscious proprioceptive (sense of position and movement) sensations.

The spino-cerebellar tracts: These are two in number, the dorsal and the ventral which lie adjacent to each other in the lateral most part of the white matter. The dorsal tract arises from the cells of the Clark's column which receive impulses along heavily myelinated fibres originating from the various proprioceptors and entering the cord through the medial division of the posterior root. The second order fibres of the dorsal nucleus, in association with a few fibres from the opposite side, ascend on the same side upto the medulla where they enter the cerebellum through the inferior cerebellar peduncle and finally end in the cortex of the anterior and posterior lobes in the cerebellum. The ventral tract arises from the cells of the chief sensory nucleus (Ranson and Clark) and after being joined by a few fibres from the opposite side, travel up to the midbrain where they arch backwards and after passing through the superior peduncle gain access to the cerebellar cortex of the anterior and posterior lobes. These two pathways are concerned with providing the afferent inflow for cerebellar control over tone and movements. Impulses travelling along spino-cerebellar tracts do not reach the level of consciousness and hence they are known as non-sensory impulses.

The spino-tectal tract arises from the posterior horn of one side and after crossing in the cord, ends in the opposite superior colliculus, thereby being responsible for spino-visual reflexes. The spino-olivary tract has the same origin and course, but terminates in the contra-lateral inferior olivary body which may relay proprioceptive impulses to the cerebellum.

Descending pathways: The most important one of these is the system of cortico-spinal fibres which forms two columns, a lateral and a ventral, in the spinal cord. Contrary to previously held ideas, these fibres arise from cells distributed over the entire cerebral cortex (60% myelinated. Of these 2%-10 to 20 μ ; 10%-5 to 10 μ ; and the rest 1 to 5 μ). The Betz cells of the motor

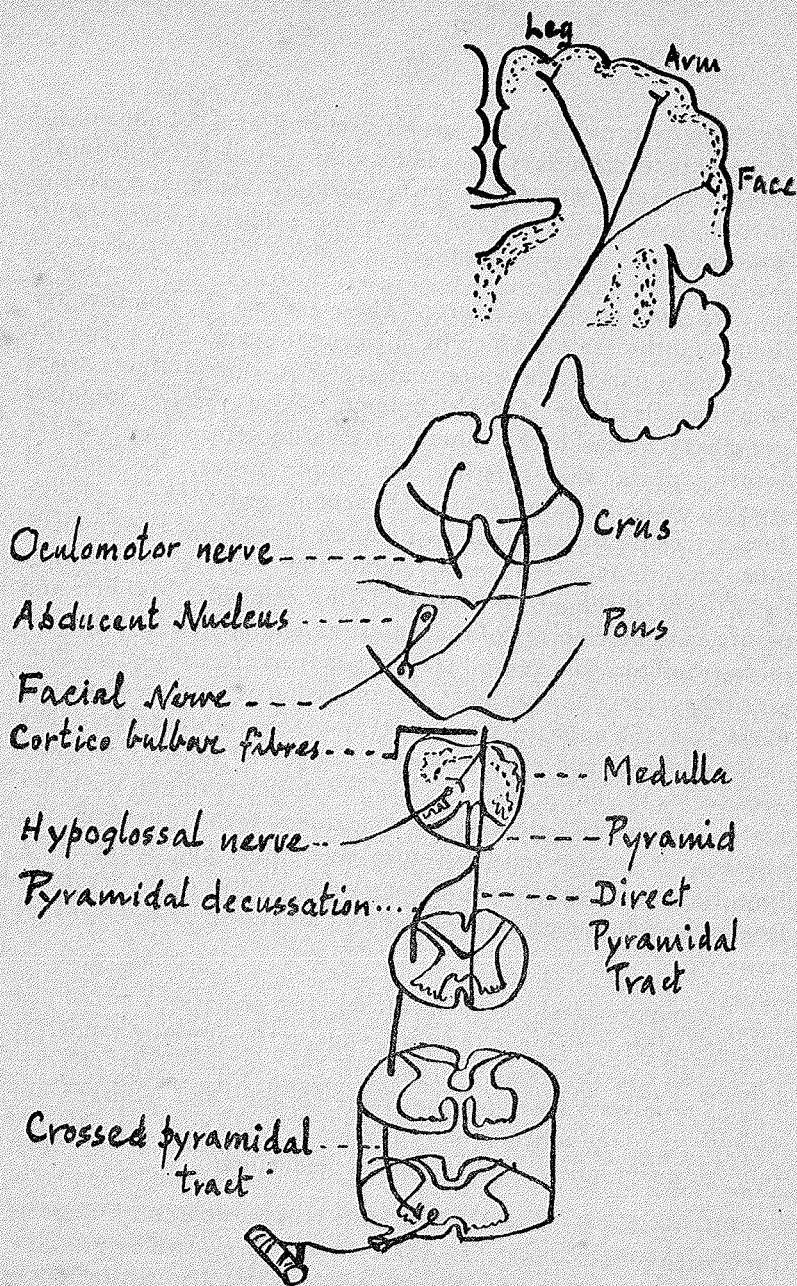


Fig. 53. The Pyramidal Tract

From Warner, E. C., Saville's System of Clinical Medicine, XIVed, (1964)
 by courtesy of Edward Arnold (Publishers) Ltd., London

area 4 account for only 3.5% (35000) of the total number of fibres (10μ diameter) of a million, in the cortico spinal pathway. This large number of fibres pass through the corona radiata and are funnelled into the internal capsule which is a band (in horizontal section) of white matter, 'V' shaped with the apex of the 'V' pointing medially. The caudate nucleus and the thalamus lie medial to the anterior and posterior limbs of the capsule respectively with the lentiform nucleus lateral to both the limbs. The cortico-nuclear fibres (those ending on cranial motor nuclei) lie in the posterior third of the anterior limb of the internal capsule. The corticospinal fibres occupy the genu and the anterior 2/3rds of the posterior limb. In the midbrain, these motor fibres form the middle 3/5ths of the basis pedunculi of the cerebral peduncles. As these descend in the midbrain and brain stem, cortico-nuclear fibres cross over at various levels to make contact with the appropriate cranial nerve motor nuclei. In the pons, the corticospinal fibres are dispersed by the pontine nuclei. They once again come together to form the medullary pyramid (giving the name pyramidal fibres). In the lower medulla, 70 - 85% cross over (motor decussation) to the opposite side to descend in the cord as the lateral corticospinal tract. The crossed fibres are believed to contain those arising from area 4. The uncrossed fibres 3-8% form the ventral cortico spinal tract and probably these arise from area 6. There seem to be some fibres even in the lateral tract which are uncrossed. 20 - 30% of the pyramidal fibres end directly on the anterior horn cells. The rest of the fibres communicate with the spinal motor neurones through internuncial neurones. Of the million fibres of each side, 55% end in the cervical region, 20% in the thoracic and 25% in the lumbar and sacral segments. It is most likely that spinal motor neurones innervating the small muscles of the hand (delicate movements) may be in direct contact with the pyramidal fibres. The pyramidal tract also contains ascending fibres, as evidenced by electrical activity in the cortex arising from medullary (pyramid) stimulation. In addition, vasodilator fibres from the motor cortex accompany the motor fibres to bring about vasodilatation of the muscles activated. The impulses from the cortex motivate the muscles and also concurrently augment the blood supply in such muscles by vasodilatation.

The vestibulo-spinal tract: It arises from the Deiter's nucleus mainly of the same side and ends either directly or through inter-nuncial neurones on the anterior horn cells, providing an efferent pathway for labyrinthine tonic reflexes acting on the limbs. The tecto-spinal tract arises from the superior and inferior colliculi of one side and cross over to the opposite side, forming at first a single bundle in the reticular formation and later, two bundles in the spinal cord. Terminations on the anterior horn cells may be direct or indirect. Visuo-spinal reflexes are mediated by this pathway. The reticulo-spinal tract arises from the reticular formation of midbrain and brain stem, some of these fibres crossing over and the others remaining uncrossed. These connect with the anterior horn cells and those of the lateral horn, providing communication from the corpus striatum, cerebellum and red nucleus. A doubt has arisen as to the existence of the Rubro-spinal tract in man. If at all present, it may not be found below the mid-thoracic region. Its function may be the same as that of the reticulo-spinal tract which may replace it.

The intersegmental tract provides connections between one segment of the cord and the neighbouring ones. The medial (posterior) longitudinal fasciculus links up the 3rd, 4th and 6th cranial nerve nuclei with each other and with the vestibular nucleus as well as with spinal motor neurones. Co-ordination of reflexes of ocular and neck muscles elicited by labyrinthine, visual and auditory stimuli, is the function attributed to this bundle.

THE STRETCH REFLEX AND DECEREBRATE RIGIDITY

A stretch or myotatic reflex is one in which a muscle exhibits a contraction when its tendon is pulled upon, stretching the muscle. Proprioceptors in the substance of the muscle belly are responsible for this reflex.

The muscle spindle (fig. 54) is a fusiform end organ, many of which are present in a muscle, the number depending on its size and importance. It consists of a bundle of about 2-7 specialised muscle fibres or intrafusal fibres with prominent striations resembling the white skeletal muscle fibres and enclosed in a connective tissue envelope. One end of the spindle is attached to the

sarcolemma of several of the fibres of the main muscle, the other end being anchored to the aponeurosis or tendon of the muscle, as the case may be. The intrafusal fibres show a zone of nuclei grouped together in their middle parts, and such regions of all the intrafusal fibres go to form the equatorial or nuclear bag region of the spindle which has a swollen appearance. The remaining lengths of the fibres at either end are designated as the myotubes. The muscle spindle has two kinds of afferent nerve supply. Thick myelinated fibres of the group I (IA) category end in the nuclear bag region, winding themselves in ring like and

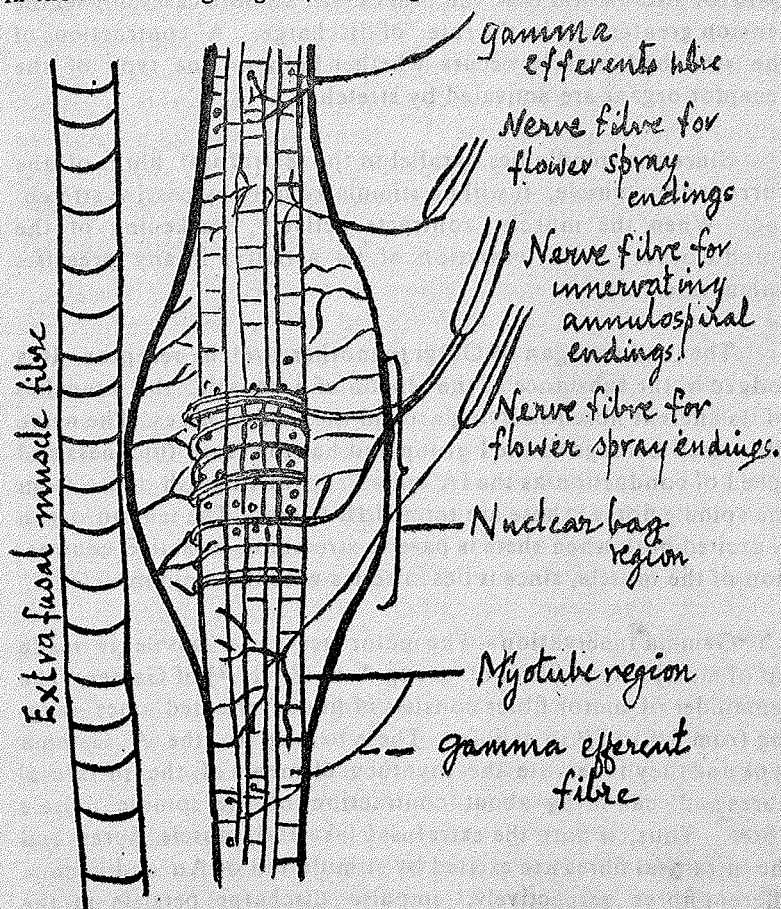


Fig. 54. The Muscle Spindle

spiral forms (annulo-spiral endings or primary endings) around the entire nuclear bag region. The second type displays a variety of ramifications but resembling roughly a spray of flowers (flower spray or secondary endings). The myelinated fibres of this end organ belong to the II group of fibres with lower velocity of conduction. Passive stretch of the main muscle puts the spindle under tension and both the nuclear bag nerve endings and the flower spray terminations are excited thereby and discharge impulses into the afferent fibres. The nuclear bag endings have a lower threshold for stimulation than the other kind. In both cases, higher the tension greater will be the rate of discharge. A contraction of the stretched muscle occurs whether both or one type of the receptor organs are activated by stretch.

Since the spindle lies parallel to the extrafusal fibres of the surrounding muscle, it will be stimulated only by passive stretching. When the muscle contracts actively, slackening of the spindle occurs with cessation of its activity, if any preexists (silent interval).

The tendon organ of Golgi is another stretch receptor. It is lodged in the substance of the tendon of a muscle, the branches of its afferent fibre ramifying around the tendon fibres. The nerve fibre itself belongs to the I group and has the same thickness and speed of conduction as the IA units. To distinguish these from the spindle fibres, these are termed IB fibres. The tendon organ is excited both when there is passive stretching or active contraction of the muscle, since it lies in series with the main muscle.

Gamma innervation – The motor nerve to a muscle is made up of a majority of fibres of group A α (8–17 μ) of Gasser. The remainder of motor fibres consists of fine myelinated ones ranging from 3 μ to 8 μ in calibre. These belong to the A Gamma type and they innervate the myotube elements of the intrafusal fibres and can bring about contraction of the spindle muscle fibres. Thus, if both the extrafusal (skeletal) muscle fibres and the intrafusal fibres are excited by stimulation of A α and gamma efferent fibres respectively, impulse discharge persists in the spindle afferents even during muscular contraction. This is so because, active contraction of the myotubes puts the nuclear

bag on stretch. Activation of the gamma efferents, while simultaneously applying tension to the main muscle, increases the force of the stretch reflex. This provides a mechanism for the augmentation of a stretch reflex.

Stretch reflex: This is a monosynaptic reflex because the afferent fibre whose cell body is in the dorsal root ganglion makes contact directly with the anterior horn cell. Consequently, the reflex delay is minimal, the reflex builds up in force suddenly and ceases also promptly. There is no after discharge. The stretch reflex is of two types— a) phasic, b) tonic. The phasic reflex is quick in onset, short in duration and is elicited by a momentary stretch. All the clinical tendon reflexes belong to this type. The tonic stretch reflex occurs when steady tension is applied to the muscle. It lasts as long as the stimulus is continued. It shows very little adaptation. This sustained reflex forms the basis of all postural mechanisms.

DECEREBRATE RIGIDITY

Sherrington produced the decerebrate state in a cat by a transverse section of the midbrain at the intercollicular level (classical type). Certain well defined and easily recognised effects were noted and these constitute the decerebrate condition. The animal adopts a broad based stance with all the limbs, neck and the tail extended, along with hyperextension of the vertebral column (caricature of the standing posture). Righting reflexes are absent and so the animal falls down when pushed to one side or the other and cannot resume its original posture. Tonic reflexes of the antigravity muscles are intensified. In the cat, these are the extensors of the limbs, tail, neck and the spinal column. In the sloth, since the animal hangs by its limbs from the branches of a tree, limb flexors are the antigravity muscles. For man, in the standing position, extensors of the lower limb and flexors of the upper limb will act against gravity. But when he assumes a quadrupedal attitude, the rigidity or hypertonicity in the proximal limb is transferred from the flexors to the extensors. Heat regulation of the body fails in the decerebrate condition. The animal cannot execute voluntary movements. The hypertonicity is reflex in origin. De-afferentation (sectioning the appropriate dorsal spinal roots) of the muscle spindles, abolishes the rigidity. Recording from

herring-gill efferents shows continuous activity of these fibres, setting up a sustained tonic state in the muscle. (see above under stretch reflex). Originally, Sherrington explained this as a release phenomenon. The modern explanation is based on the activity of the two systems of descending fibres of the recently discovered reticular formation. The inhibitory fibres of this system arise at a cortical level and make contact either through the caudate nucleus by relay or directly, with the brain stem facilitatory reticular fibres, thereby normally suppressing their facilitatory activity. Inhibitory influences also originate in the anterior lobe of the cerebellum which controls the bulbar inhibitory reticular fibres. The vestibular nucleus forms part of the facilitatory system and by its descending fibres (vestibulospinal tract) can facilitate stretch reflexes. Formerly when less was known about the reticular formation, it was tacitly assumed that the removal of the influence of red nucleus as by an intercollicular section, was the cause for rigidity. It was shown later that localised destruction of this nucleus did not produce marked rigidity. Destruction of the vestibular nucleus, on the contrary, reduced the hypertonicity considerably. So it has to be inferred that when the brain stem facilitatory fibres and the vestibular nucleus are freed from the inhibitory control of the cerebral cortex and the caudate nucleus, hypertonicity of the antigravity muscles will be caused. It also follows that the brain stem facilitatory system predominates over the brain stem inhibitory system. Gamma fibres to the spindle are made to send a constant barrage of impulses by the facilitatory reticular neurones.

Pollock and Davis produced decerebration by depriving the major portion of the brain, of its blood supply by tying the vertebral arteries and the basilar artery at the pontobulbar junction. This is the so-called ischemic decerebrate preparation. This condition is due to the increased activity of the $A\alpha$ motor innervation to the extrafusal muscle fibres. In this case, deafferentation does not cause the rigidity to disappear.

In Sherringtonian rigidity, cooling or ablation of the anterior lobe of the cerebellum intensifies the already existing hypertonicity. Contrarily, stimulation of the same part of the cerebellum lowers the degree of tonicity of the muscles. It is believed that

the anterior lobe of the cerebellum is responsible for switching over from gamma activity to that of alpha neurones. Cooling the cerebellum alters the basis of the rigidity from hyperactivity of the gamma neurones to hyperactivity of the alpha neurones. In other words, Sherringtonian rigidity is changed to that resembling the ischaemic type of Pollock and Davis.

THE COMPLETE TRANSVERSE SECTION OF THE SPINAL CORD

This subject has assumed importance because of injuries sustained by not only men of the armed forces but also civilian casualties of bombing of the cities and towns during the two world wars. Observations made on subjects with spinal cord injuries, have led to the development of steps and techniques for not only prolonging the lives of injured people but also to make their existence, as far as possible, pleasant or tolerable. Transverse section of the spinal cord has been performed in experimental animals with a view to gaining an insight into the mechanisms responsible for the symptoms which are usually described as coming on in three stages one after the other.

1. **Stage of loss of reflexes:** All the muscles innervated by the spinal cord below the level of lesion are completely paralysed, the reflexes involving them being lost thereby. There is also a total sensory loss. The walls of the bladder and the rectum are completely atonic and their respective sphincters either retaining their tone or recovering it after a very brief period of paralysis. In the case of lesions affecting the higher reaches of the spinal cord, the blood pressure will show a severe fall but if the injury is below the lumbar level, such a fall will not occur. The venous return to the heart is therefore impeded as a result of hypotension. All these features are referred to as spinal shock. The mode of injury has no bearing on the causation of spinal shock. Only those parts of the body which are supplied by nerves arising from the cord distal to the site of injury, show features of spinal shock which appears to be due to interruption of nervous influences arising at higher levels in the brain and controlling the activities of the spinal cord. Spinal shock is of very brief duration in lower animals which recover within a very short time - less than an hour in the rat, cat and dog. In the monkey, it lasts for several days.

In the human patient, it has a much longer duration. Greater the encephalisation of nervous functions, the longer will the spinal shock last.

2. Stage of restoration of reflexes: Hollow viscera, like the rectum and the bladder, regain their tone and so also their sphincters if they had been affected initially. At first retention may occur and may have to be relieved by catheterisation which is a very important nursing procedure. It not only helps to empty the bladder but also prevents troublesome infection of the urinary tract. If blood pressure has suffered a fall in the first stage, it tends to reattain its original level on account of the regaining of tone by blood vessels as a result of the spinal vasoconstrictor centre regaining its control.

The muscles gradually regain their tone, the flexor muscles earlier than the extensors. That is why flexor reflexes return first. In the case of the monkey or man, a typical Babinski's sign which is really a withdrawal reflex, is unmasked. This reflex (see elsewhere) may affect all the joints upto the hip and may include abduction of the thigh also.

In some animals or human patients, an abnormal response—the mass reflex, may be observed. Stimulation of any point on the lower limbs or even on the abdominal wall brings about widespread effects. Both lower limbs exhibit strong flexion. The bladder and the rectum may empty themselves. Intense sweating of the affected parts of the body is also seen. With efficient modern nursing, the mass reflex may not be seen in human subjects. Even when mass reflex is present, it makes its appearance only some months after the injury.

The deep reflexes are re-established in stages. Thus, the knee jerk may, in the beginning, be seen as a hardening of the quadriceps muscle. Later on, the full reflex can be elicited. Even so, the reflex ends abruptly, the stretched muscle relaxing suddenly.

The extensor reflexes return somewhat late. When the flexors are stretched, the extensors go into a tonic contraction, thereby even supporting the weight of the body.

Reflex emptying of the bladder and the rectum are re-established. Sweating appears in the affected parts and the skin temperature may rise.

3. If proper nursing care has not been bestowed, spreading infection and toxæmia supervene. The reflexes fail once again and the muscles waste. The condition of the patient or animal becomes aggravated and deterioration sets in rapidly.

When the lower limbs are paralysed along with involvement of the bladder and the rectum, the condition is one of paraplegia. After complete transection of the cord, since flexors regain their tone earlier, the lower limbs are held in flexion and the condition is one of paraplegia in flexion.

After spinal cord injuries, in which the vestibulo-spinal and the reticulo-spinal tracts are spared, extensor tone is retained and extensor reflexes are prominent. Such a condition is termed paraplegia in extension.

BROWN-SEQUARD SYNDROME

Brown-Sequard syndrome: This comprises of symptoms arising out of a hemisection of the cord. In humans, the lesion is usually a tumour pressing upon one side of the cord, though later it may involve the other side also culminating in an incomplete and still later complete interruption of the cord.

The symptoms are due to the involvement of both sensory and motor pathways and they are different on the two sides of the body. The accompanying table presents the important features of this clinical condition.

Sensory

	same side as the lesion	opposite side
a) At the level of lesion	Hyperaesthesia and hyperalgesia may occur if the injury is not of the type of a clean surgical incision.	———

- | | | |
|------------------------------|---|--|
| b) Below the level of lesion | Pain and temperature sensations are retained. Touch sense blunted. Deep sensations like vibration sensibility and sense of position are lost. | Pain and temperature sensations lost. Touch somewhat affected. Deep sensations retained. |
|------------------------------|---|--|

It is needless to mention that there are no sensory symptoms above the level of lesion on either side.

Motor

- | | | |
|------------------------------|--|------|
| a) At the level of lesion. | If an appreciable number of anterior horn cells are affected, a flaccid paralysis of muscles with attendant trophic disturbances may be seen (L. M. N. type) | ———— |
| b) Below the level of lesion | A spastic paralysis along with brisk tendon reflexes and an extensor plantar response are seen. | |

A recapitulation of the courses of spinal tracts will enable one to account for the above-mentioned features of Brown-Sequard syndrome.

HEMIPLEGIA

The descending motor system of fibres of the pyramidal tract and the cortico-nuclear fibres (given off to the cranial nerve nuclei) are liable to be affected by lesions at certain points or locations in their course, especially where they form compact bundles very vulnerable to damage. The most common effect of such lesions of the motor fibres is a paralysis of the opposite half of the body (hemiplegia) with or without involvement of cranial motor nerves also.

When a vascular lesion such as haemorrhage, thrombosis or embolism occurs in the internal capsule, the whole of the

opposite half of the body including the face will exhibit muscular paralysis. If the lesion is in the midbrain, the III nerve nucleus of the same side (as that of the lesion) and the opposite half of the rest of the body (including the opposite 5th and 7th nerves) will be paralysed. This condition is referred to as Weber's syndrome. Involvement of fibres lower down in the pons may affect the ipsilateral 6th and 7th nerve nuclei (face paralysed on same side) along with paralysis of the contralateral half of the body (Millard—Gubler's syndrome). Lesions in the medullary decussation of the pyramids affect only the opposite half of the body without facial involvement at all.

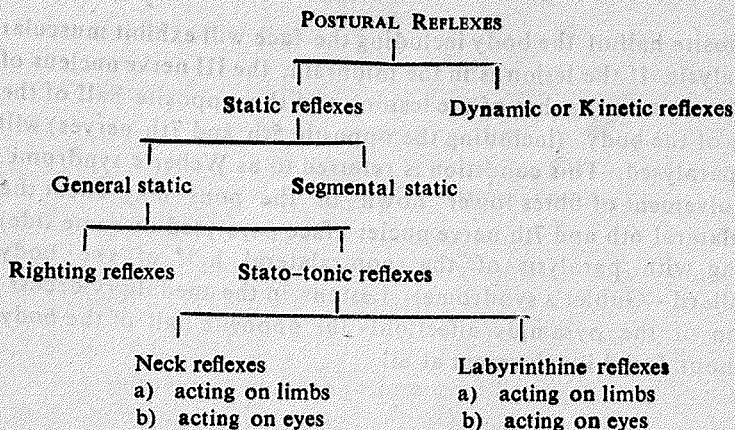
In all the above cases, if supranuclear fibres or upper motor neurones are affected, the paralysis will be of the spastic type with brisk tendon reflexes and extensor plantar response. In the case of midbrain and pontine lesions, when the ipsilateral 3rd nerve nucleus or the 7th nerve nucleus respectively are affected, the ocular and facial muscles exhibit flaccid paralysis characteristic of lower motor neurone lesions.

THE POSTURAL MECHANISMS

A variety of reflexes result from the stimulation of several types of receptors in the body and these are all directed towards bringing about, in an animal -

1. The proper orientation of the head in space.
2. The correct relationship between the positions of the head and the trunk.
3. The movements of the limbs and the eyes resulting in appropriate relationship between them and the head for the particular position of the head.

These mechanisms have been studied by Magnus and De kleijn. The different reflexes responsible for the various adjustments necessary to adopt a new posture and to maintain it, are as follows:



Righting reflexes: These come into play when the position of the body and the head is disturbed and they effect the correct orientation of the head and body in relation to each other in the newly adapted position. These are five in number and can be easily observed in all animals. They can be demonstrated in a decorticate or thalamic animal which retains the righting reflexes. The decerebrate preparation is devoid of these reflexes.

1. **Labyrinthine reflex acting on the neck muscles:** When a rabbit is held by the pelvis and is suspended from it, the head is raised so as to assume a position it would have if it were sitting. Impulses originating in the maculae of the utricle and saccule while the head was in the dependent position, bring about the contraction of the neck extensors to orient the head in the correct position in space. Destruction of the labyrinths abolishes this reflex and the head hangs down as in a dead animal. Visual sensations can mitigate the loss of labyrinths so that appropriate correction is possible. Even a new born baby, if held by the pelvis, will exhibit this reflex. Fish deprived of the labyrinths and eyes, cannot swim in the correct position. When they touch a solid object in water or the sides of the pond or tank, they can resume their normal position. Deafmutes, even if they can swim, may be drowned if they dive deep into water, as neither visual nor labyrinthine reflexes can come to their aid. The visual reflexes are absent inside water, as vision is very limited or absent. These subjects have functionless labyrinths (inner ears) which cannot evoke righting reflexes.

2. Neck righting reflexes acting on the body: If an animal is laid on its side on a table, the head assumes the normal position. This is followed by the turning over of the body to result in the sitting or crouching position. The influence of neck reflexes on the body in its resumption of the sitting posture or that of lying in the prone position, is due to the proprioceptive impulses arising in the neck muscles when they contract to set right the position of the head. The muscles of the trunk and limbs are now activated in order to correct the position of the body.

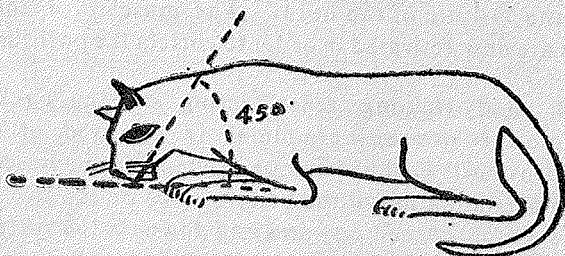
3. Body righting reflex acting on the neck: If in the example cited above, the animal is deprived of its vestibular apparatus, still the head can be brought into correct orientation. Unequal stimulation of the body surface on the two sides caused by the weight of the body pressing down on the surface in contact with the table, is responsible for this restitutory reflex. If a wooden board of a weight equal to that of the animal is placed on the free surface of the body, this righting reflex can be suppressed, since both sides of the body are subject to the same stress.

4. Body righting reflex acting on the body: In an animal placed on its side, if the head is held down, the body can still correct itself to assume the sitting posture. This again is due to unequal stimulation of the two sides of the body and can be prevented in the same way as indicated under (3).
5. Visual righting reflexes: Labyrinthine reflexes are normally reinforced by visual reflexes which can be effective even if the former are put out of action. An individual can always correct the position of his head or body with the aid of visual sensations.

Stato-tonic reflexes: A decerebrate preparation is suitable for eliciting these responses though they may also be seen in normal animals. Labyrinthine tonic reflexes can be studied in isolation by immobilising the neck by a plaster collar or by cervical posterior root section. Contrarily, neck reflexes can be unmasked by keeping the head immobile as in a clamp, to render labyrinthine mechanisms ineffective. The influence of the neck reflexes produce opposite effects on the fore and hind limbs. When the neck is flexed, flexor tone is marked in the forelimbs

while extensor tone is increased in hind limbs. When extension of neck occurs, forelimbs are extended and hind limbs go into flexion. These responses can be seen in an animal like the cat, as it looks up at a bird in a tree (neck extended) or looks from a height at a mouse below (neck flexed). The characteristic positions of the limbs can be noted.

A.



B.

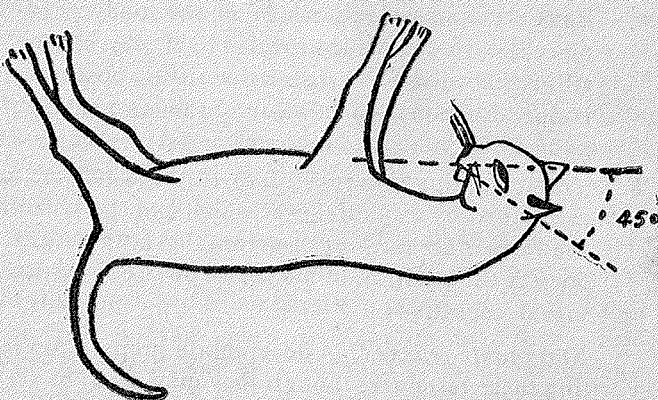


Fig. 55. Labyrinthine tonic reflexes (see text)

Labyrinthine tonic reflexes, on the other hand, exert the same effect on all the limbs (fig. 55). The rise in extensor tone or flexor tone in all the limbs will depend on the position of the head (in other words labyrinth) which is denoted by the angle, the mouth cleft (line of contact of the upper and lower jaws) makes with the

horizontal. In the prone position of the animal, when the angle is 45° above the horizontal, flexor tone is marked in all the four limbs. When the animal is lying on its back with its mouth cleft at 45° below the horizontal, marked extension of all the limbs is noticed. For intermediate positions between two extremes, the tone will be between the two extremes. Pressure on the seventh cervical vertebra causes reduction of tone in all limbs. When an animal, while walking, turns its head to one side, the limbs on that side (jaw limbs) are extended but the contralateral limbs (skull limbs) are flexed and withdrawn from the ground to be placed in a new position to support the body which is being turned. When both labyrinthine and neck reflexes are operating together, the effects of the latter predominate.

Tonic reflexes, both of the neck and labyrinthine kinds, acting on the eyes bring about movements of the eyes in a direction opposite to that of the head movement. When the head is turned to the right, the eyes are directed to the left. When the face is turned downwards, the eyes are rotated upwards. As long as the new position of the head is maintained, so also will be that of the eyes. Here, the actual movement of the eyes is due to a statokinetic reflex arising out of excitation of the semicircular canals. Holding the eyes in the new position to conform to the altered position of the head, is due to a statotonic mechanism maintained by utricular stimulation.

The centres for the various postural mechanisms described so far, are as follows :

1. Righting reflexes except the visual reflex—in the midbrain.
2. Visual righting reflex—cortex
3. Statotonic labyrinthine reflex acting on limbs — vestibular nucleus
4. Statotonic neck reflex acting on limbs — upper three cervical segments of the cord.
5. The tonic reflexes acting on the eyes — centre situated between the vestibular nuclei and the motor nuclei of the extraocular muscles.

Placing and hopping reactions: When an animal moves about, it is enabled to place its paws in appropriate positions to

support the body. These placing movements are effected by the stimulation of exteroceptors in the skin and proprioceptors in the muscles and joints. In animals like the cat, the vibrissae on the face may also be responsible for placing reactions. When an animal is pushed to one side or the other, the limbs are abducted or adducted so as to be kept under the corresponding shoulder or hip in order to prevent a fall. Myotatic or stretch reflexes are involved in these hopping reactions. The cerebral cortex of the sensory and motor areas are responsible for bringing about these adjustments.

Local static and segmental reactions : The withdrawal of a limb in response to a painful stimulus applied to it (flexion reflex) involves only one or two spinal segments and as such it is a segmental or local static response. The crossed extensor reflex-extension of the opposite limb, accompanies the flexion of the stimulated limb—is also an example of a segmental static reaction.

When an animal places its foot pad on the ground, both the flexors and extensors of the limb contract reflexly to make the limb like a rigid pillar to support the weight of the body (positive supporting reaction). These effects are due to the stimulation of the proprioceptors in the flexors of the joints of the limb and consequent myotatic reflexes in these muscles. These in turn evoke similar stretch reflexes in the extensors as well.

The stretch reflexes are reinforced by the excitation of pressure receptors in the foot pad (pressing on the ground).

When the foot or the limb is lifted from the ground, the limb is flexed at all joints and withdrawn (negative supporting reaction). These movements are initiated by the plantar flexion at the distalmost joint which, in its wake, stretches the more proximal flexors and a series of flexion movements at more and more proximal joints follows.

Stato-Kinetic mechanisms are dealt with under 'Labyrinth'

THE LABYRINTH AND THE VESTIBULAR APPARATUS

The labyrinth derives its name from labyrinthos – the word from the Greek legend, denoting a maze or medley of passages and chambers. The bony labyrinth is lodged in the petrous

part of the temporal bone (the densest bone in the body) well protected from injury and to prevent direct mechanical insults to the delicate proprioceptive end organs in it. It comprises two ovoid chambers, (Fig. 56). the utricle and the saccule and three semicircular canals. The delicate membranous labyrinth has the

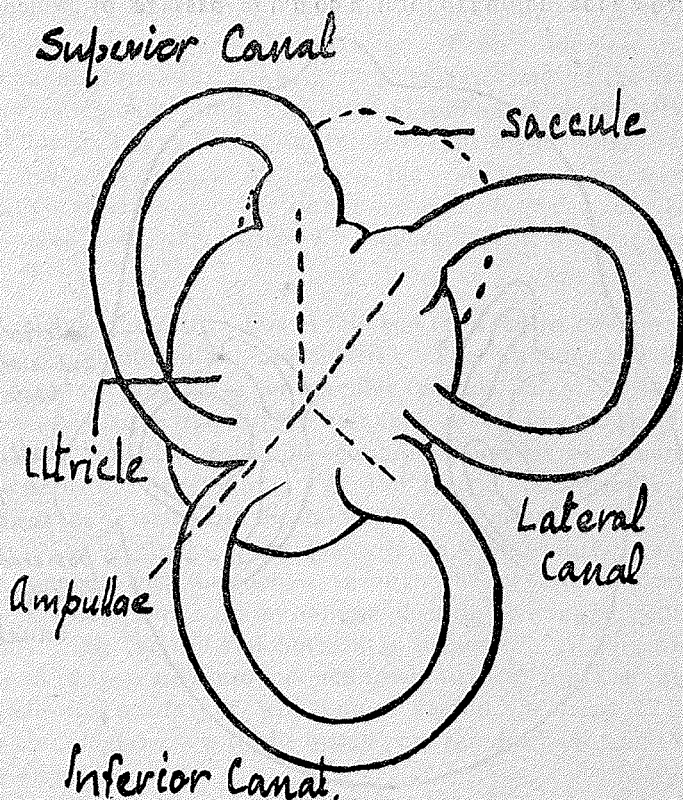


Fig. 56. The Right Labyrinth (diagrammatic)

same shape as the bony labyrinth which it occupies, though the former is of much smaller dimensions. Filling the bony labyrinth is the perilymph, a fluid of nearly the same composition as the cerebrospinal fluid. The perilymph surrounds the membranous labyrinth which contains a different fluid, the endolymph, resembling in its constituents, the intracellular fluid. Semicircular canals:— There are three—a horizontal (lateral) and two vertical

canals, the superior (or the anterior) and the inferior (or the posterior) (Fig. 57). Each canal has one end narrow and the other expanded (the ampulla) in which is present the end organ, the crista. The horizontal canals have their ends opening into the utricle separately, while the vertical canals have their narrow ends uniting to form a common passage by which they

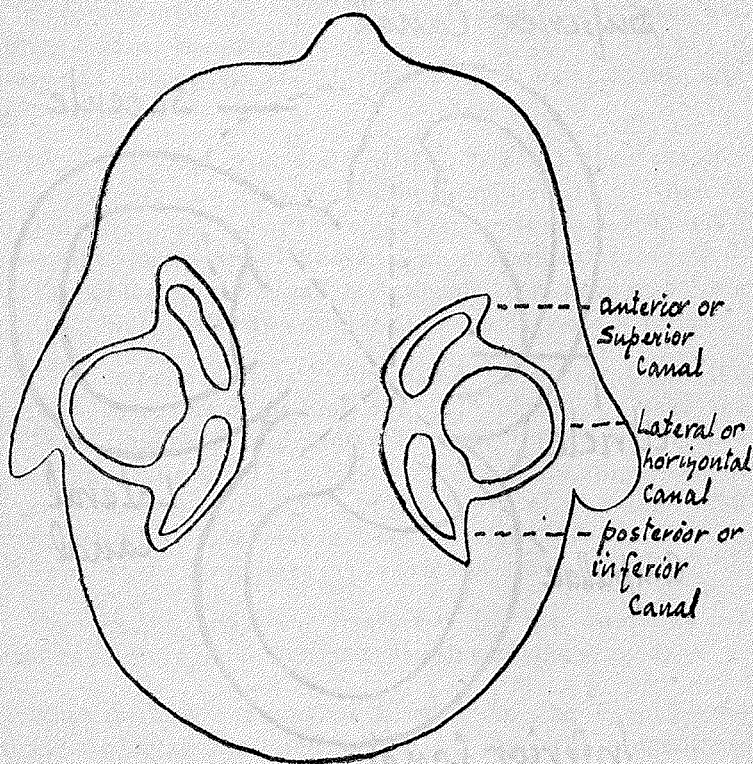


Fig. 57. 'Position' of Semicircular Canals (much enlarged) in head as seen from above.

communicate with the utricle. But their ampullary ends open each by itself into the utricle. The horizontal canal is in a plane facing backwards and upwards forming an angle of 30° with the horizontal. The anterior and posterior canals, make an angle of 45° with sagittal plane and frontal plane (of the skull) respectively, so that the anterior canal on one side is parallel to the posterior canal of the opposite side but at right angles to its counterpart on the opposite side.

Ampullae are present in the three canals in positions indicated as follows – anterior end of the horizontal canal, anterior end of the superior canal and the posterior end of the inferior canal. The crista, one in each ampula, is made of a mound of connective tissue covered by sensitive hair cells whose long hair-like processes (cilia) are all embedded in a dome-like structure (the cupula) made of jelly-like material. Each cilium lies in a narrow canal of its own in the cupula. The basal ends of the hair cells are in contact with the peripheral processes of the nerve cells (of Scarpa's ganglion) in the internal auditory meatus. The central processes of these cells form the vestibular division of the eighth cranial nerve. The ampullary ends of the semicircular canals open into the utricle by separate communications, one for each.

Utricle and Sacculæ : The utricle and the sacculæ communicate by the ductus utriculosaccularis. The utricular and the saccular sense organs are called maculae (macula-singular). Each is formed of a plaque of sensitive hair cells covered by gelatinous material—the otolith membrane—containing crystals or concretions, the otoliths or otokonia. In the utricle, the macula is situated on the anterior and medial walls which meet at an angle of 140° . The hair cells point laterally and posteriorly. The sacculæ connects with the cochlea through the canalis reuniens and the hair cells here have an oblique position forming an acute angle with the vertical and horizontal planes. The saccular maculae of the two sides are inclined towards each other so that if extended backwards they would meet behind the head. The sacculæ communicates with the utricle on the one hand and the cochlea on the other.

Nervous connections of the labyrinth : Central connections are widely distributed throughout central nervous system and have not been fully worked out. Cell bodies of vestibular nerve lie in the internal auditory meatus and form Scarpa's ganglion. The cells are bipolar in shape and their dendrites are distributed to hair cells in maculae and cristae. The axons pass to the superior, lateral, medial and inferior vestibular nuclei. The superior nucleus relays fibres to medial longitudinal bundle of same side ; the medial nucleus to the opposite medial longitudinal fasciculus. From the inferior nucleus, fibres go to medial longitudinal

fasciculus of both sides. These fibres end in third, fourth and sixth cranial nerve nuclei, forming vestibulo-ocular tract. The movements of the eyes in response to head movements are brought about through this pathway. Descending fibres from lateral vestibular nucleus and inferior vestibular nucleus form the vestibulospinal tract. The inferior vestibular nucleus sends fibres through the medial longitudinal fasciculus to the upper cervical part of the spinal cord. Fibres from lateral nucleus pass through the inferior cerebellar peduncle to reach the flocculonodular lobe and fastigial nucleus of the same side, forming the vestibulo-cerebellar tract. Impulses conveyed along this path and then through the cerebellar peduncle to temporal lobe cause the sensation of vertigo. The fibres from vertical canals, after passing through the vestibular nuclei, divide into two diverging paths at the pons – one to the medial longitudinal bundle and the other to the cerebellum through the middle cerebellar peduncle.

Effects of unilateral labyrinthectomy :

- 1) Eyes are turned to the side of lesion. On the affected side, the eye turns downwards and on the opposite side the eye turns upwards (skew deviation). Horizontal nystagmus with slow component to operated side is another (see below) feature.
- 2) Lateral flexion and rotation of the occiput to the operated side with flexion of the thorax on pelvis towards the other side.
- 3) Extensor tone is greater on the opposite side.
- 4) Spontaneous movements – circling, rolling, etc.
- 5) Head nystagmus, falling towards operated side and stepping gait.

Nystagmus, rolling movements are due to irritation and disappear after some time. But other symptoms persist, though later they may be compensated for, in higher animals, by visual and other reflexes as well as by cortical control. Bilateral ablation causes effects same as above, on both sides. The labyrinthine static reflexes are abolished but visual reflexes compensate in righting mechanisms. Normal reaction (see below) to rotation is abolished.

Labyrinthine functions :

Semicircular canals generate impulses for 'dynamic' sense. Maculae subserve static sense mainly and dynamic sense to a less extent. The cristae respond to angular acceleration (on rotation). The maculae are stimulated by changes in the position of head and linear acceleration and they are also gravity receptors, since vertical movement of the head stimulates them.

The semicircular canals: Continuous rotation does not cause an excitation, but only acceleration or deceleration. Canals are only 0.1 to 0.2 mm in diameter and the endolymph is viscous (twice or thrice the viscosity of water). The membranous labyrinth is a closed system and supported by perilymph outside. When head is rotated to the right, in the beginning, due to angular acceleration, the cristae of the semicircular canals in the plane of rotation get stimulated. Due to inertia of endolymph on account of high viscosity, the hair cells are bent in the reverse direction (left). When the swing of the cupula is towards the macula, stimulation of that crista results. The opposite crista is inhibited (swing away from the macula) – i. e. – the rotary receptors are stimulated when the narrow part of the canal leads and ampulla trails. In vertical canals, however, the opposite is the case. Each canal is stimulated by rotation not only in its plane, but also in other planes to some extent. When rotary movement is continuous, the inertia of endolymph is overcome and stimulation ceases. But on cessation of rotation, deflections of hairs occur in the opposite direction. So, an illusion of rotation in opposite direction, occurs. No receptors responding to continuous rotation are present in the labyrinth, because it is not a natural movement. The head is rarely subjected to such stimuli.

Mode of stimulation of the semicircular canals: The semicircular canals can be stimulated — 1) by rotation of head about a vertical, transverse or anteroposterior axis. 2) by caloric stimulation – syringing cold or warm water into ear. 3) by galvanic current, 4) by raising or lowering the pressure in the perilymph by means of a plunger placed in the bony vestibule (mechanically).

Effects of stimulation are — 1) eye movements, 2) vertigo, 3) reactions of neck and limb muscles, 4) autonomic reactions,

1) *Eye movements* : Rotation of about 10 turns in 20 seconds stimulates semi-circular canals (horizontal) in a person with head erect. But for maximal stimulation, head should be slightly inclined forward, by 15° . The subject has his eyes closed during rotation, but opens them after sudden cessation of rotation. The eyes exhibit to and fro motion, a slow turn to one side and a quick return to the original position. Nystagmus lasts for 20 seconds, normally. Quick component is opposite to the direction of rotation and slow component in the same direction as that of rotation, in post-rotatory nystagmus. Nystagmus is named after the direction of the quick component. Vertical and rotatory nystagmus will occur when both vertical canals are excited at the same time. Vertical nystagmus is induced when the plane of rotation is the same as the sagittal head plane, with head inclined at about 90° to one side or the other. Rotary type occurs when head is bent forward or backward during rotation. Post-rotary nystagmus occurs when the head is brought to normal position. The slow component has a centre in the vestibular nucleus, from which impulses go to the nucleus of 3rd, 4th and 6th cranial nerves. Quick movement is entirely central in origin and the nerve pathway is not known. The centre may be in the brain stem between and including third nerve and vestibular nuclei. Cerebellar ablation does not abolish it. Probably, the quick component may have a centre in the 6th cranial nerve nucleus. Possibly, a pathway exists between the vestibular nucleus and ocular nuclei through the reticular formation also.

2) *Vertigo* : This is a whirling sensation or sense of giddiness with disturbance of equilibrium. If head is erect during rotation, vertigo is in horizontal plane, but in a direction opposite to that of rotation (sensation of counter rotation). After rotation is stopped, the individual feels that he is falling to the opposite side, due to 'reverse' stimulation of semi-circular canals, especially when head is bent forward at 90° to stimulate vertical canals during rotation. After rotation, if head is not brought to the upright position, counter rotation in horizontal plane is felt. But, if head is brought to the upright position, a sensation of falling to the side opposite to that of rotation, occurs. Rotation with head bent backward and then brought to the upright position, gives a sensation of falling to same side. The sensation of falling forward

or backward results from rotation with head flexed to one shoulder or the other and then brought upright. Vertigo can occur in conditions other than rotation – seeing objects from a train, sea sickness, eye strain and Meniere's disease. Whatever may be the nature of the stimulus, stimulation of semi-circular canals or their central connections, is the immediate cause of vertigo.

3) *Reaction of neck and limb muscles:* When horizontal canals are stimulated by rotation, the tone of muscles on the opposite side of the body (on right side when rotation is to left) is increased, the head turns to the opposite side due to increased tone of neck muscles. The right limbs are flexed and the left limbs are extended. Reverse changes occur when movement is stopped. A quick tilt forwards and to the right causes flexion of the right forelimb. A tilt backward and to the right causes flexion of the right hind limb.

The Past-pointing test of Barany: A normal person can place his finger on a spot with eyes closed, once he has seen it before. After rotation, he cannot do the same with eyes closed. The finger deviates or 'past-points' to one side or another. It is due to a voluntary act, based on an error in judgment which is a consequence of vertigo, an overcorrection made in the direction opposite to that of vertigo. The finger deviation and vertigo are in opposite directions. The subject, in trying to adjust his position in the light of his false sensation of falling to one side, falls to the opposite side. Disc throwing or discobolus attitude is seen after rotation and more readily after cold caloric test or galvanic stimulation. It is due to reflex alterations in the tone of muscles on the two sides of the body.

4) *Autonomic reactions:* Parasympathetic effects like fall in B. P., bradycardia, pupillary constriction etc., occur during rotation. On stopping, sympathetic effects are seen. Stimulation of central end of the cut vagus after labyrinthectomy, causes a fall in B. P. but normally a rise occurs. After unilateral labyrinthectomy, stimulation of the central end of the cut vagus nerve causes fall on that side with decrease in limb volume. Labyrinthectomy may result in inhibition of vasoconstrictor centre. The limb volume falls due to draining of blood.

Caloric Stimulation: The canal chosen to be stimulated should be in the vertical plane. The advantage of this mode of excitation is that each canal can be stimulated separately. Warm water at 112°F or cold water at 68°F can be used. With warm douche, the convection currents set up will flow away from the site of stimulation. With cold douche, the flow will be toward the site of stimulation. So, appropriate responses – nystagmus and vertigo – will result. Horizontal canals are stimulated with head bent 60° backwards. Vertical canals are excited when head is in erect position.

Galvanic stimulation: All canals are simultaneously excited by this method. Nystagmus may be rotary as well as horizontal. When the cathode is over the right labyrinth, nystagmus is to the right and to the left when the cathode is on the left side of the head. The effects occur only at make and break. The cristae are directly stimulated by the current. Even if the vestibular nerve is directly stimulated, it will give rise to similar effects. The cupula is not deflected during electrical stimulation.

Mechanical stimulation: Increasing the pressure in the perilymph (outside the membranous canal) or decompression is the means of stimulation. Endolymph movements are caused which stimulate the semicircular canals,

The maculae are excited when there is a bending of the cilia of the sensitive cells in one direction or even when there is a pull on them, as by gravity in the upside down position of the head. Angular acceleration may also stimulate them though not so effectively as the cristae. The sacculle has been regarded more as a part of the hearing apparatus though it cannot be absolved of responsibility in signalling changes in the position of the head. In fact, the saccular macula may respond to tilting of the head to one side or the other. The macula on the side to which tilt has occurred, sends greater number of impulses than the opposite one and thereby furnishes the information required. Upward linear acceleration excites both saccules to the same extent. Utricles are instrumental in providing information regarding downward or horizontal acceleration as well as tilting of the head forwards or backwards.

Disease and vestibular reaction: Spontaneous vertical nystagmus may occur with brain stem lesions. It is not seen in labyrinthine or nerve disease.

Meniere's disease: Paroxysms of vertigo, tinnitus and perceptive deafness occur, sometimes with loss of consciousness also. Spontaneous horizontal nystagmus is also seen. Pressure alterations or chemical changes in the composition of endolymph are thought to be the most likely causes. The volume of endolymph is also increased. It is surgically treated by the section of the vestibular nerve only, leaving intact the cochlear division.

Labyrinthine fluids: The perilymph communicates with the subarachnoid cistern through cochlear aqueduct or canaliculus whose opening into the labyrinth is barred by a limiting membrane of arachnoidal origin. A valve is said to exist between saccus endolymphaticus and utricle, allowing only flow into the latter but not in reverse direction. The saccus is thought to have a secretory function and fluid from it may pass into utricle and semicircular canals and function independently of cochleo-saccular portion of membranous labyrinth. Alternatively, saccus may have absorptive function and a valve may not exist either. Protein content of endolymph and perilymph is more than that of cerebro-spinal fluid. But Na^+ and K^+ of perilymph differ little from cerebro-spinal fluid. In endolymph there is more of K^+ and less of Na^+ . In perilymph $\text{Na}^+ = 148 \text{ mE/L}$ and $\text{K}^+ = 4 \text{ mE/L}$. Reverse in endolymph. Non-protein nitrogen in perilymph and endolymph is not different from that in cerebro-spinal fluid. Some authors deny protein disparity. But higher protein content of perilymph suggests presence of a semipermeable membrane between perilymph and cerebro-spinal fluid. Perilymph may be a stagnating fluid due to restriction in cerebrospinal fluid circulation. Endolymph resembles intracellular fluid of high K^+ and low Na^+ content and is probably produced by secretion by specialized cells, though where exactly the secretion occurs is not yet known. This high K^+ content and low Na^+ content may have a bearing on nerve impulse transmission in the tunnel of Corti, where only endolymph is present and how nerve impulses can be conducted in a fibre bathed in endolymph

with high K^+ content, is not known. In this regard, endolymph is different from other extracellular fluids (rich in Na^+) which surround nerve fibres.

THE RETICULAR FORMATION

Reticular formation is unlike other circumscribed and easily identifiable parts of the brain and is made of a diffuse collection of nerve cells of various sizes and shapes and large numbers of nerve fibres running in different directions. Recognisable anatomical entities like the red nucleus, substantia nigra and subthalamus are excluded by definition from the reticular formation, though functionally these structures are very much associated with this system of cells and fibres which extends throughout the brain stem, in the medulla, pons and the midbrain and even to the thalamus and hypothalamus in its rostralmost portions. Caudally, it is continuous with the internuncial neurones of the spinal cord.

Magoun and Rhines investigated the functions of the reticular formation by means of discreet stimulation of its various parts. In general, they found that stimulation of points in the ventromedial part of the lower medulla resulted in inhibition of the stretch reflexes as well as the disappearance of decerebrate rigidity. With weak stimuli, the effects were unilateral, but with increase in the strength of stimulation, bilateral effects were obtained. From more laterally situated points in the medulla, facilitatory effects like augmented knee jerk were elicited. The facilitatory area extended upto the midbrain tegmentum and even the subthalamus.

The phenomenon of decerebrate rigidity was explained as due to the unopposed action of the facilitatory parts of the reticular formation. The inhibitory components seemed to need, for sustaining their action, impulses from the cerebrum and cerebellum and in a classical decerebrate preparation, the inhibitory areas were deprived of their input from the cerebral cortex. The facilitatory areas, on the other hand, do not have to depend on a drive from higher neural levels. Their activity is maintained by the afferent impulses arising in the proprioceptors including the vestibular end organs.

In decerebrate rigidity, it is the antigravity muscles (mostly extensors) that exhibit hypertonicity, which is attributed to facilitatory influences from the reticular formation. As shown by Sprague and Chambers, the terms facilitatory and inhibitory should not be taken to mean that the tone of all muscles is affected in the same way, when either facilitation or inhibition occurs. Facilitatory areas of the reticular formation, when excited bring about a rise in the tone of the extensor muscles (antigravity) and a reduction in flexor tone. Inhibition of facilitatory areas affects the muscles in the opposite way.

One mode of action of the descending reticular system (both facilitatory and inhibitory components) is to alter or modify the activity of the gamma motor neurones innervating the fusimotor fibres of the muscle spindle and thereby influence the tone of muscles. The alpha motor activity is controlled by the motor area of the cortex. In conclusion, it may be said that the extra-pyramidal system which originates in the cortex and is relayed by the basal ganglia to be finally linked up with the spinal motor neurones by means of the brain stem reticular formation, appears to have a direct effect on the spinal motor neurones, in addition to its influence on gamma motor neurones.

Even prior to the discovery of the role of reticular formation in the regulation of muscle tone it was known that the neurones of the brain stem reticular formation were responsible for the control of visceral functions, circulatory and respiratory adjustments and also temperature regulation. These aspects have been touched upon in relevant chapters.

The Ascending Reticular Activating System and Wakefulness

The work of Bremer (see Sleep) led to the modern concept of the mechanism underlying sleep, of Moruzzi and Magoun, who interpreted Bremer's findings in the Cerveau Isolé preparation.

The reticular system has an ascending counterpart to the descending facilitatory and inhibitory divisions. The ascending reticular activating system commences in the lower brain stem and reaches upto the thalamus and eventually to the cerebral cortex (see Thalamus). Even in this, there are two divisions or routes which the impulses take. One is by way of the

subthalamus and therefrom directly to the cortex. The other is through the midbrain and the intralaminar, midline and the reticular nuclei of the thalamus and finally to the entire cerebral cortex.

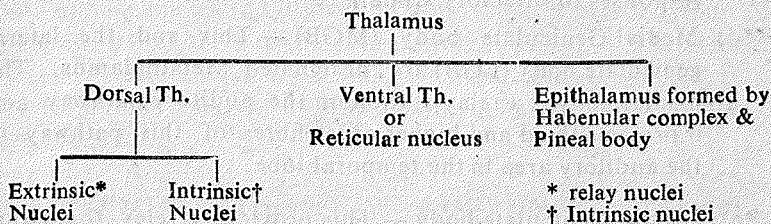
Stimulation of the upper reaches (pontile and midbrain regions) of the ascending reticular system caused a sleeping animal to awaken (arousal). On the other hand, lesions placed in this region brought on coma like states. It has been observed that the excitation of the brain stem portions of this system causes widespread activation of the cerebral cortex as well as that of many subcortical areas and nuclei, like the basal ganglia and even the spinal cord. The effect is of an intense degree and outlasts the stimulus and as such the brain stem portion is held to be responsible for the arousal response and for the subsequent wakeful state. Stimulation of this portion gives rise to two sets of impulses, one coursing through the subthalamic region directly to the cortex and the other indirectly, being relayed by the thalamic nuclei. The latter set of impulses have two effects – one is to bring about a widespread activity in the cortex and the second is to excite certain specific areas. It is this last mentioned action that enables to channel one's mental activity in a particular and chosen direction.

In a sleeping animal (synchronous electrical activity as seen in the EEG), a stimulus to any receptor can bring about an awakening response (desynchronisation), but proprioceptive or painful stimuli are most effective. The continuance of the wakeful state, once it is set up, is the result of the interaction between the cortex (of various areas) and the ascending reticular system itself. Reverberating or oscillatory circuits are set up and the impulses travel cyclically between the thalamus and the cortex. There is also a positive feedback mechanism in operation. The rise in activity in the ascending system increases that of the cortex which in turn raises the level of activity of the reticular fibres and so on. When there is a decline in the afferent discharge to the cortex, the feedback from it to the reticular activating system also suffers a diminution and the reverberating circuits become quiet, bringing on sleep.

THE THALAMUS

This is a large ovoid mass of grey matter lying across the cerebral peduncles, separated from its fellow on the opposite side rostrally by the 3rd ventricle and caudally by the Corpora Quadrigemina.

Based on the nerve fibre connections and the anatomical location, it is divided into different nuclear groups as follows :



The epithalamus has no known function.

Extrinsic Nuclei of Dorsal Thalamus: Five groups are described.

- *a) **Posteroventral**—This is the chief sensory relay station for all the sensory pathways excepting that of smell. All the fibres forming the medial, spinal and trigeminal fillets in the brain stem terminate here. There is an orderly arrangement of fibres, as evidenced by strychninisation studies—fibres from face and mouth end medially, next will be those from the upper limb and most laterally are those from the lower limb. In lower animals, the medial most part of this nucleus goes by the name arcuate nucleus. Taste fibres from the nucleus solitarius end in the inner most part of this ventro-medial mass. The final link of the somato-sensory pathways arises in this nucleus and makes connections with the parietal cortex.
- *b) **Lateroventral** – This nucleus receives fibres arising in the dentate nucleus of the cerebellum (dentatothalamic tract) as well as the red nucleus. The projections from here are given off to the motor areas 4 & 6 of the cerebral cortex. The cerebellar control of the cortically originated motor activity

is effected through these connections. Ataxia and muscular weakness associated with thalamic lesions (syndrome) are explained on this basis.

- *c) Anterior Nucleus receives afferent fibres (Tract of Vic d'Azyr) from the mamillary bodies of the hypothalamus. Efferent fibres make contact with the paracentral lobule and area 24 in Cingulate gyrus on the medial surface of the cerebrum. This pathway mediates visceral and autonomic responses to olfactory stimuli.
- *d) Medial Geniculate body (MGB) — This and the lateral geniculate body (LGB) are designated Metathalamus. The medial body is a relay station on the auditory pathway and it projects third and higher order fibres of this pathway to the auditory area in the temporal lobe.
- *e) Lateral Geniculate body — This provides a relay for visual fibres to finally end in the calcarine area in the occipital lobe.

†*Intrinsic nuclei* : These are five in number.

1. Midline nucleus.
2. Intralaminar nuclear group. Subdivisions of this are :
 - a) Centrum
 - b) Centromedian
 - c) Centrolateral
 - d) Paracentral
 - e) Parafascicular
 - f) Limitans.

These cell groups are not so well developed in primates as in lower forms.

3. Dorsomedial Nucleus
4. Dorsolateral
5. Pulvinar — attains greatest development in primates.

The nerve fibre connections of the intrinsic nuclei are as follows :

The midline and the intralaminar nuclei send fibres to the frontal lobes, hypothalamus and the neostriatum. The dorsomedial nucleus connects up with the frontal lobes and the hypothalamus. The dorsolateral nucleus and the pulvinar give off projections to the parietal lobes of the cortex. The

intralaminar group degenerate after cortical lesions. They receive fibres from the tegmentum, tectum of the midbrain as well as the reticular formation of the brain stem and in turn establish contact with the Ventral thalamic mass.

Ventral Thalamus—This consists of a thin shell of grey matter covering the dorsal portion of the thalamus on its anterior and lateral aspects. It derives its afferent connections from all the intralaminar nuclei and it gives off a diffuse nonspecific system of thalamocortical fibres to the entire cerebral cortex. The ventral thalamus has been called the reticular nucleus in view of its being pierced in many places by the main thalamocortical sensory projections.

Functions of the thalamus: As a relay station in the ascending sensory pathways, it serves as the highest centre for awareness of crude sensations which are further elaborated at the cortical level. In lower animals it, along with the corpus striatum, integrates all automatic and instinctive movements such as those involved in courting and fighting. In birds, the well coordinated flight manoeuvres are attributed to the joint control by thalamus and corpus striatum.

Studies with strychninisation of the thalamus have amply shown the detailed spatial or somatotopic representation of the body surface in the posteroventral nucleus. Further, hyperesthesia and hyperalgesia to superficial stimuli results, especially on the opposite side of the body. Increased sensitivity to deep stimuli is seen only on the opposite side.

Perhaps the thalamus is the highest centre for the perception of pain.

By virtue of its association with the ascending reticular formation and its widespread connections with the whole of the cerebral mantle, it is responsible for the arousal phenomenon. Further, by the constant activity of the reverberating thalamocortical circuits which are kept humming, it is concerned with the maintenance of the wakeful state. Impulses in the reticular system set up widespread electrical activity of the cerebral cortex, as seen in electroencephalograms.

Effect of thalamic lesions: Whenever the relay nuclei, especially the posteroventral nucleus and the lateroventral nucleus, are affected by loss of blood supply as happens in a vascular accident, certain symptoms appear. Muscular weakness, loss of tone and incoordination of muscles result. Also, the discriminative aspects of sensations suffer. These features which are seen in the opposite side of the body can be explained on the basis of the efferent connections of the two nuclei. Astereognosis (see parietal lobe under Cerebral Cortex) also is seen.

Spontaneous pain may occur, coming on in bouts. Even ordinary cutaneous sensations acquire unpleasant overtones. The affected side of the body is peculiarly prone to react in an abnormal way to ordinary innocuous stimuli. All the above mentioned symptoms comprise the thalamic syndrome.

THE HYPOTHALAMUS

The diencephalon consists of the thalamus and hypothalamus in addition to the subthalamic nucleus and others. The hypothalamus forms the basal part and is separated from the thalamus, by the subthalamic sulcus. The hypothalamus consists of nuclei in the lateral walls and floor of the third ventricle. Anteriorly, it extends to a limit slightly rostral to the optic chiasma and

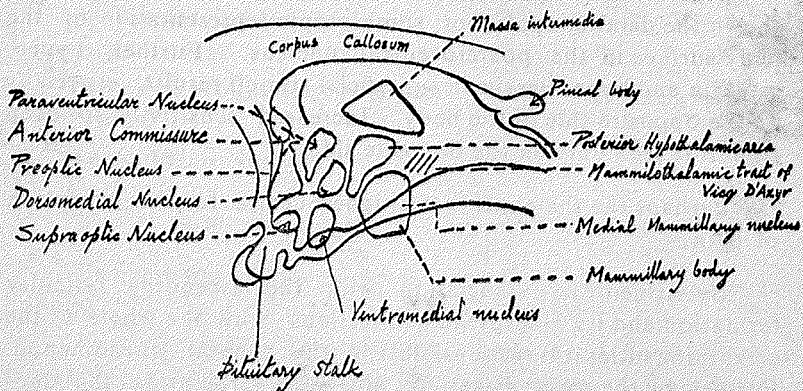


Fig. 58. The Hypothalamus

From LeGros Clark, *The Topography and Homologies of the Hypothalamic Nuclei*, J. Anat. (Lond.) 70, 204, 1936.

caudally, till the mammillary bodies. Ventrally, the hypophysis (the neurohypophysis) is suspended by the pituitary stalk from tuberal region of the hypothalamus. The nerve cells in the hypothalamus form three groups of nuclei.

- 1; Anterior — Preoptic Nucleus } in close relation to
Supra optic nucleus } the optic chiasma.
2. Middle — Dorso medial nucleus
Ventromedial ,,
Lateral ,
Tuberal ,,
3. Posterior — Mammillary bodies
Posterior nuclei.

The hypothalamus has rich to and fro connections with the rest of the brain. The incoming fibres will be formed by:—

- a. Median forebrain bundle containing fibres from the prefrontal lobe (orbitofrontal areas), olfactory and paraolfactory areas, septal region, ending in all parts of the hypothalamus. The supraoptic and paraventricular nuclei receive fibres from the prefrontal areas and premotor areas through the thalamus and directly also.
- b. Fibres from Globus pallidus.
- c. The fornix from the hippocampus, terminating in the lateral mammillary bodies.
- d. The stria terminalis from the amygdaloid body.
- e. Fibres from the intrinsic nuclei of the thalamus.
- f. Collaterals of various sensory ascending pathways of the brain stem including taste fibres.

The outflow from the hypothalamic nuclei is made up of

1. Mamillothalamic tract of Vicq d'Azyr from the medial mammillary body to the anterior nucleus of the thalamus.
2. The hypothalamico-hypophysial tract linking the supraoptic and paraventricular nuclei with the neurohypophysis and possibly the intermediate lobe as well.
3. Fibres to the cerebral cortex through the thalamus and other routes.
4. Descending fibres from the anterior group and the posterior group which end on the brain stem cranial nerve nuclei (parasympathetic control system) and the cells of the medio-lateral column of the spinal cord (sympathetic control) respectively.

The functions of the hypothalamus ;

1. **Control of autonomic nervous system:** The descending connections of the anterior group of nuclei (along with tuberal nuclei) with the peripheral parasympathetic fibres and those of the posterior nuclei with the dorso lumbar sympathetic outflow, provide the highest subcortical control of the vegetative nervous system. Stimulation of the hypothalamus in the anterior part gives rise to effects like fall in blood pressure, fall in heart rate, increased gastro-intestinal motility, augmented secretions of the digestive glands, pupilloconstriction etc., similar to the excitation of peripheral parasympathetic fibres. Likewise, sympathetic effects of pupillodilatation, tachycardia, peripheral vasoconstriction etc. were elicited by the activation of the posterior part of the hypothalamus. Thus, the two functions of the hypothalamus have been termed as *ergotropic* — directed towards increased expenditure of body reserves of energy, as in fight or flight reactions resulting from the mobilisation of the sympathetic nervous system and *trophotropic* — helping to build up the stores of energy in the body which is the effect of parasympathetic activity.
2. **Temperature regulation:** The anterior and posterior regions of the hypothalamus function together as a thermostat in the maintenance of the body temperature. The heat loss centre is in the forepart. Stimulation here will bring forth responses like sweating, peripheral vasodilatation and panting in animals like the dog. Even warming this region calls forth these reactions. Lesions placed in the 'rostral' hypothalamus renders the animals helpless against a rise in external temperature, the animal going in for hyperthermia—raised body temperature. The mechanisms promoting loss of body heat are put out of action. Normally the heat loss centre is provoked into action by warm blood coursing through it and also by nerve impulses arriving from the peripheral 'warmth' receptors. Of the two factors, the direct effect of warm blood on the hypothalamus seems to provide a crude control, while the peripheral stimuli yield a fine control. Likewise, the heat production and conservation centre is influenced by direct cooling by blood flowing in that part as well as by

impulses arising from cutaneous receptors for cold. Damage to the posterior nuclei may make the animal poikilothermic. Thermoregulation fails and the animal attains the environmental temperature. The descending fibres from the heat loss centre will be interrupted in such a case. Rarely, heat production only may be affected whereby piloerection, peripheral vasoconstriction, shivering and release of adrenaline will be suppressed, marked fall in body temperature or hypothermia supervening. The co-ordinated activity of the centres in the hypothalamus is necessary for homeothermia or maintenance of the normal body temperature.

Control over food intake: Hetherington and Ranson produced bilateral lesions of the hypothalamus in animals in the region of the ventromedial nucleus and found hyperphagia leading on to obesity, as a consequence. Stimulation, on the other hand, resulted in cessation of feeding even in hungry animals. This led these workers to postulate the existence of a 'satiety centre' located in the ventromedial nucleus. A feeding centre was believed to exist in a position lateral to the satiety centre. Stimulation of the second centre (Delgado and Anand) caused the animal to eat voraciously even when it had been fed previously. Contrarily, injury to this centre made the animal turn away from food even while starving. Of the two centres, the satiety centre seems to control the activity of the feeding centre. The so called 'glucoreceptors' on excitation, (in hyperglycaemia), bring about the sensation of satiety by activating the satiety centre. They are inhibited by hypoglycaemia and hence depress the satiety centre. A rise in blood sugar stimulates the satiety centre but suppresses the activity of the hunger or feeding centre. Mayer, who fathered this glucostat theory, attempted to explain the causation of hunger in both diabetes mellitus and hyperinsulinism. In the diabetic condition, glucose is unable to enter and excite the glucoreceptors in the absence or deficiency of insulin. In hypoglycemia, due to excess insulin action, the blood sugar level is too low to enable the glucoreceptors to abstract it from blood. In either case, the effect would be that of hypoglycemia which activates the hunger centre and depresses the satiety centre. Against this hypothesis is the fact that nervous tissue which obtains energy from glycolysis does so even in diabetes mellitus, in the absence of

insulin, glucose entering the cell with ease. An earlier hypothesis of Brobeck, based on the working of a 'thermostat' which caused either hunger or satiety to occur depending on the non-production or production of heat by way of specific dynamic action, has some points in its favour. Rats seem to choose foods which have a greater specific dynamic action, in preference to ones with less. When gold thioglucose was administered to mice, it caused a selective destruction of the ventromedial nucleus; such animals showed marked obesity subsequently. It is concluded that the glucoreceptors in the satiety centre were rendered ineffective by the toxic accumulation of gold along with the innocuous glucose for which the receptors have such avidity. The hunger centre had a free and unfettered activity, increasing the food intake, thereby producing obesity.

Role in water balance: The action of the antidiuretic hormone (ADH) in the regulation of water balance has already been touched upon in the discussion under the neurohypophysis. A rise in the crystalloid osmotic pressure in the extracellular fluid, exerting its action on the so-called osmoreceptors in the region of the supraoptic nucleus brings forth the release of the ADH which promotes reabsorption of water in the distal convoluted and collecting tubules of the kidney. Water is conserved in the body in order to lower the raised osmotic pressure. In the opposite case of water logging in tissues, ADH secretion is suppressed so that water can be lost in greater amounts in urine. It has been seen that electrical stimulation of the hypothalamus in goats by electrodes implanted in the region between the fornix and the mammillothalamic tract, induced excessive drinking of water resulting in overhydration and rise in body weight. Injection of minute amounts of hypertonic saline in the same region also called forth the same response. Such facts go to show that water intake is also regulated by the hypothalamus in the maintenance of water balance in addition to controlling the output of urinary water.

Control of gastric secretion: Stimulation of the anterior nuclei evoked immediately a profuse and sustained secretion of acid rich gastric juice. Activation of posterior hypothalamic area also caused secretion but with a longer latency and maintained

for a longer period. While vagus was the efferent channel for the first effect and vagotomy abolished this effect, it had no effect on the second mode of secretion. Hypoglycemia arising out of insulin action may bring about gastric secretion both by a neural and a hormonal mechanism. The arousal of the appetite occurs concomitantly with the secretion of gastric juice, in preparation for the reception of food in the stomach. Gastric ulcers may result from prolonged and intense hypothalamic stimulation. Emotional factors are known to be a predisposing cause of gastric ulcers and hypothalamus is definitely involved in the pathogenesis of peptic ulcers.

Sleep and hypothalamus: Sleep can be induced in animals by stimulating the hypothalamus in the neighbourhood of the *massa intermedia* of thalamus or even the intralaminar nuclei. This is unexpected since the reticular formation which connects with the intralaminar nuclei, is responsible for the arousal or waking response of a sleeping animal. Hypothalamus and the thalamus are implicated in the causation and cessation of sleep.

Control of the secretory activity of the adeno-hypophysis: Attention has already been drawn to this aspect of hypothalamic function in the chapter on the pituitary gland. The hypothalamus liberates releasing factors under the influence of nervous impulses arising from diverse sources. Each releasing factor put forth under the appropriate stimulus is conveyed in the blood flowing in the hypothalamico-hypophyseal system, to the anterior pituitary lobe where it brings about the secretion of the relevant pituitary principle. In the case of prolactin however, the hypothalamus secretes an inhibitory factor (PIF). The negative feedback mechanism, by which the blood levels of the hormones of the target glands of the hypophyseal hormones prevent further release of the pituitary factors, may partly operate by exerting an influence on the hypothalamic output of the releasing factors themselves and to some extent by a direct action on the adeno-hypophysis itself. It is not possible at the present juncture to state which of these two modes of feedback control is more important. There are indications to suggest that action through hypothalamic route may be more sensitive. (see pituitary). Recent work, making use of

animal tissue extracts from various regions of the hypothalamus, strongly indicates that each of the releasing factors may specifically be elaborated by a particular area in the hypothalamus. The neighbourhood of the supraopticohypophysial tract may be responsible for the elaboration of the thyrotrophin releasing factor, as evidenced by stimulation experiments as well as effects arising out of lesions located here.

Hypothalamus and sex functions. It is well known that in the lower mammals, environmental factors are responsible for initiating sex functions. Exposure to light as occurs under a bright summer sun, brings on the changes associated with oestrus or the reproductive phase of sex life. The mere sight of the partner is sufficient, as in the pigeon and in some cases, copulation is necessary for ovulation to occur, as in rabbits. Such important changes in the sex life are known to be effected through the agency of the hypothalamus. Neurohumoral reflexes arising out of peripheral stimulation (visual stimuli, excitation of the genital tract by mating) bring in their wake, release of the hypothalamic humoral factors which in turn influence the adeno-hypophysis to liberate its own gonadotrophic hormones that ultimately affect gonadal activity. Destruction of the tuberal region of the hypothalamus interrupts this complicated neurohumoral pathway. Prolactin and oxytocin output are known to occur as a result of the suckling reflex. This action is also mediated through the hypothalamus.

Hypothalamus and the neurohypophysis: There are well established nerve connections between the supraoptic and paraventricular nuclei on the one hand and the neural lobe of the pituitary gland on the other. There is much evidence to show that the so called neurohypophysial factors are really elaborated by the neurosecretory cells in the hypothalamus itself and these are only stored in the gland to be liberated into blood stream whenever necessary. The fibres of the hypothalamico-hypophysial tract and the cells of supraoptic and paraventricular nuclei themselves show the presence of the 'Gomori' substance believed to be the hormones themselves. These nerve fibres show the presence of vesicles similar to presynaptic vesicles. Section of the pituitary stalk causes the

accumulation of the secretory material proximal to the cut. The absence of secretory elements among the cell constituents of the posterior pituitary lobe and the blind termination of the nerve fibres ending in the 'gland', are additional facts to favour the view that it is only a storage organ for the hormones.

Hypothalamic role in relation to emotion and reactions arising therefrom: An animal (cat) deprived of its cortical hemispheres, presents a characteristic picture of 'sham rage' (coined by Bard) or a pseudoaffective state (Sherrington). The cat is not consciously angry and hence the term. Even the slightest of inconsequential stimuli brings forth the vigorous responses of rage – spitting, snarling or growling, lashing of the tail, protrusion of the claws, sweating, erection of hair, faster respiration, raised blood pressure, biting and struggling. These responses are now believed to be not due to the loss of the cerebral cortex, but of certain parts of the rhinencephalon on the medial aspect of the cerebral hemisphere – pyriform lobe, amygdaloid nucleus and hippocampus, in addition to the zone of transitional cortex under the cingulate sulcus. Retention of the rhinencephalon prevents the unmasking of the rage reaction. Such a preparation manifested itself as a very placid and docile creature tolerating even painful stimulation. Removal of even parts of the rhinencephalon changed the animal completely into one which became ferocious on the slightest pretext. The rhinencephalon, it is therefore concluded, exerts a restraining influence on hypothalamic reactions for expression of anger, in dogs and cats. The wild rat and the monkey, however, after an operation like removal of the amygdaloid nucleus, present a marked contrast. These become tame, very placid and amiable and actually show signs of pleasure as a reaction to stimulation. While consciousness of displeasure or resentment or anger resides in the cortex, the visible visceral and bodily manifestations arise out of the excitation of the hypothalamus.

Syndromes arising out of hypothalamic disorders :

It is now understood that in all pituitary disorders, the hypothalamus may also be implicated. Diabetes insipidus, dystrophia adiposo genitalis and other conditions are usually described as hypothalamico hypophyseal disorders. Certain special states

as mentioned below may be the outcome of hypothalamic dysfunction.

- 1) Narcolepsy - a subject of this condition shows a disturbance of the sleep pattern. The duration of sleep is very brief and he takes naps very frequently even in day time when he is at work. Other features of hypothalamic disease like obesity, sexual infantilism and polyuria may co-exist with this condition.
- 2) Cataplexy-emotional upset precipitates a state of helplessness arising out of muscular weakness and prostration. Usually, light-heartedness or mirth triggers off this condition. This disorder always accompanies narcolepsy and is never seen by itself in isolation.
- 3) Catalepsy-A very peculiar condition is catalepsy, in which the afflicted individual can assume statue like attitudes. Limbs, when placed in particular positions can be held so, for prolonged periods without onset of fatigue.

THE EXTRAPYRAMIDAL SYSTEM

The pyramidal system of motor fibres arises from a widespread region of the cerebral grey mantle and is held to be the main, if not the exclusive, pathway for motor activity. Extrapyrarnidal fibres also originate from the cells of the cerebral cortex over an equally wide area. Particularly, these contain the outflow of the so called suppressor areas of the cortex 2s, 4s, 8s & 24s. Voluntary movements are also effected through this system of fibres which do not have direct contact with spinal motoneurons. They form a multi-synaptic descending pathway on which many subcortical nuclear groups including the basal ganglia, feature as relay stations. The most rostral of these fibres deriving directly from the cortical cells themselves and synapsing at a lower level with basal ganglia and other nuclear masses, in other words, the cortical components, have been named as the 'Cortically originating Extrapyrarnidal system' (COEPS). These link up with cells in the corpus striatum, thalamus, substantia Nigra, red nucleus, pontine nuclei and even the brain stem reticular formation. Even when lesions are placed in the area 4 of the cortex or section is made of the medullary pyramids, it is still possible, in primates, to bring about

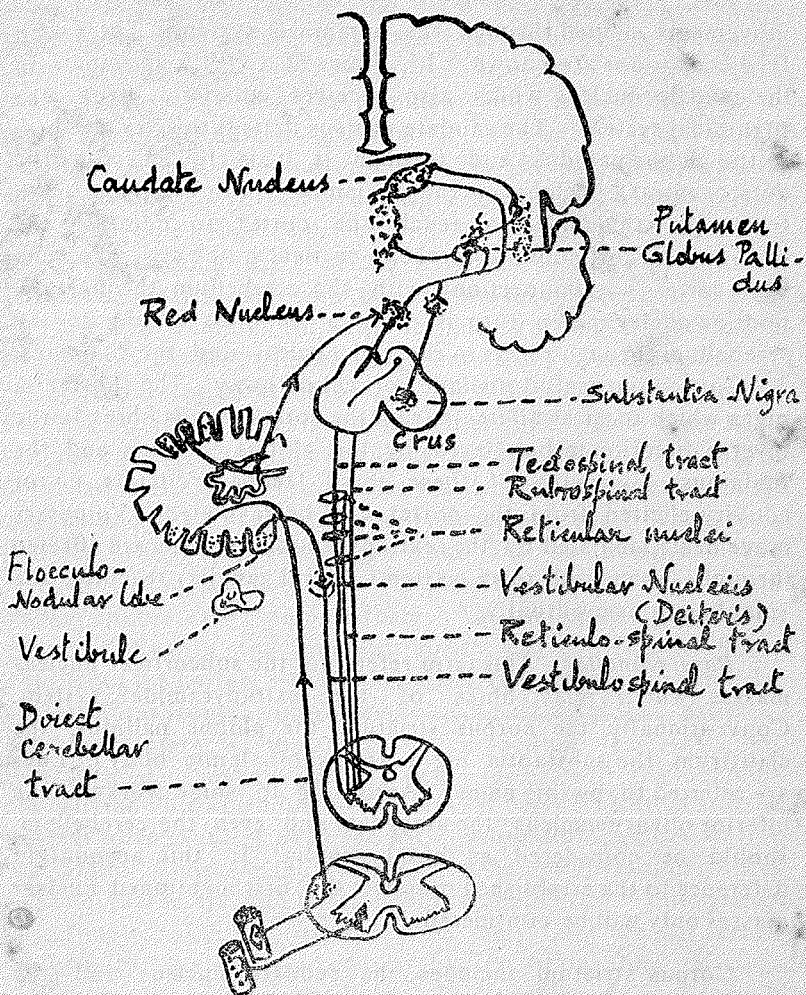


Fig. 59. The Extra-pyramidal Tracts

After Warner, E.C., Saville's System of Clinical Medicine, XIVed.
 Orient Longmans Ltd., New Delhi, P. 1045 by Courtesy of Edward
 Arnold (Publishers) Ltd., London.

voluntary muscular activity, though skilled and delicate movements are lost. Strangely however, this cortically originating system also provides a restraining or inhibitory action on

movements elicited through the pyramidal system. Three such feed back loops are known. 1. Fibres of COEPS terminate in the caudate nucleus which also receives collaterals from the pyramidal system. The caudate nucleus in its turn gives off fibres to the globus pallidus and through it, it is linked with the anteroventral nucleus of the thalamus. Fibres issue forth from the thalamus to reach the cortex to complete the circuit. 2. Corticoponto-cerebello-cortical pathway. The cerebral cortex has connections with the cerebellum through the pontine nuclei and in turn it receives impulses arising in the cerebellum through relays in the red nucleus and the thalamus. 3. Corticonigropallidothalamocortical pathway. The substantia nigra which receives afferents from the cortex, sends fibres in the reverse direction to be relayed by the globus pallidus and the thalamus. By means of these three feedback circuits, motor activity elicited from the cortex can be regulated. Voluntary movements mediated by the extrapyramidal system are effected through subcortical relay systems (basal ganglia) reaching the spinal neurons eventually.

Basal Ganglia: This term refers to the subcortical nuclear masses which relay fibres of the extrapyramidal system. Conventionally, the corpus striatum, the globus pallidus, the claustrum, the substantia nigra and subthalamic body of Luys are referred to, by this name. According to some workers, the inferior olivary nucleus, the amygdala and even the cerebellum, should be considered as basal ganglia. In this account, in deference to the established practice, the first mentioned nuclear masses only will be considered.

Corpus striatum includes the caudate nucleus and the putamen, the lateral most division of the lentiform nucleus. The caudate nucleus is an elongated structure with a pear-shaped head, a long body or tail ending in the amygdaloid nucleus caudally and inferiorly. The globus pallidus is the medial part of the lentiform nucleus and it itself is made up of lateral and medial portions. The anterior limb of the internal capsule, a V-shaped (in horizontal section) band of white matter, lies between the head of the caudate nucleus and the lentiform nucleus. Streaks of grey matter can be seen between the two structures and hence the term corpus striatum. In each of the structures

that could be brought under the term basal ganglia (with the exception of cerebellum), there are two histologically differentiated parts — a small celled division (nucleus Parvocellularis - phylogenetically of recent development) and a large-celled portion (nucleus magnocellularis—older part). Afferent fibres end in the nucleus parvocellularis and the outflow of efferent fibres arises in the large celled part. Of the basal ganglia mentioned in the beginning, the caudate nucleus and the putamen receive fibres from various other parts of the nervous system. The caudate nucleus receives fibres from the suppressor areas 2S, 4S and 8S and it relays to the brain stem inhibitory reticular formation through the globus pallidus. The putamen is a relay centre for fibres from the cerebral motor areas 4 & 6 which are connected with the excitatory reticular formation of brain stem. These have internal connections with the globus pallidus through which are funnelled the outgoing fibres (ansa lenticularis) to the other basal ganglia and the thalamus (anteroventral nucleus). The globus pallidus, the substantia nigra and the subthalamus have reciprocal connections between each and the other two, so that a closed circuit exists among them. The thalamus not only has efferent links with the cerebral cortex, but also receives fibres back from the cortex. The red nucleus (nucleus parvocellularis) derives fibres from the precentral lobe of cortex, globus pallidus, substantia nigra, subthalamus and cerebellum. Efferent fibres from it (nucleus magnocellularis) communicate with the thalamus rostrally and the ascending brain stem reticular formation and the inferior olive caudally and even with oculomotor nucleus in the mid brain. Thus, the red nucleus links the extrapyramidal fibres at the higher levels with the terminal components of this system. In primates, the rubrospinal tract may not be of much importance. Its role is taken over by the brain stem reticular formation with which it has links. The profuse point to point connection between the thalamic intralaminar nuclei (centromedian, paracentral and centrolateral) and the head of the caudate nucleus suggests that the neostratum (putamen & caudate nucleus) depends functionally on the thalamus and in lower animals, these two along with globus pallidus (paleostriatum) form a sensory motor integrating system.

Functions of the basal ganglia: It is rather difficult to pinpoint the role of these subcortical nuclear masses, especially

in primates. In the carnivora which have only rudimentary or imperfectly developed cerebral cortex, the corpus striatum acts as the highest motor area and is responsible for instinctive and automatic motor activity as well as voluntary movements. The loss of the neocortex does not cause any motor defects in such animals. On the contrary, in the primates, total removal of the cerebral mantle abolishes all voluntary muscular activity. If the cerebral grey matter is removed piecemeal with adequate post-operative care, volitional motor activity can be re-established to a large extent, the extrapyramidal system compensating for the loss of the classical cortico-spinal pathway. Nevertheless, fine and skilled movements are irrevocably lost.

Stimulation experiments have yielded results which cannot be interpreted easily. Excitation of the neostriatum brought about cessation of cortically induced phasic (rapid) movements. But from the globus pallidus a 'plastic' reaction was obtained. Limbs were held in particular positions, though this could be passively changed into newer attitudes which were also maintained.

Ablation of the corpus striatum as well as the globus pallidus did not bring about abnormal involuntary movements like chorea, athetosis or tremors which are seen in diseases of the basal ganglia. In fact, thermoelectric coagulation of the globus pallidus or sectioning the ansa lenticularis causes troublesome tremors and other movements and rigidity to be reduced or to disappear. If the area 6 of the cortex is also simultaneously damaged along with the lentiform nucleus and the caudate nucleus, rigidity develops in muscles. Tremors are believed to result when the fibres descending from the level of the red nucleus to the medial reticular formation are sectioned, the neurones in the reticular formation becoming sensitised to circulating acetyl choline, giving rise to tremors. The use of atropine to minimise tremors is explained on this basis. Interruption of corticospinal fibres, damage to motor cortex, or cerebral peduncles, or spinal tract, abolish tremors.

According to Ward, an oscillatory discharge to muscles originates in the reticulospinal tract below red nucleus which is not inhibited by the higher components of the extrapyramidal

system - viz from substantia nigra. Interruption of the cortical circuit passing through caudate nucleus and thalamus will relieve the patient of his tremors. It follows that the oscillatory activity responsible for tremor may arise in this loop.

In conclusion, it may be suggested that the role of basal ganglia is twofold. 1) They may control or modulate the activity of the cerebral motor areas directly or by means of convergence of fibres at a lower level. 2. Alternatively, these may act in a synergistic way on spinal neurones independently of the cortical motor areas.

There are several clinical syndromes resulting out of lesions of the basal ganglia. The better known ones are: Parkinson's disease, chorea, athetosis, hemichorea or hemiballismus, and and torsion spasm.

Parkinson's disease (Parkinsonism): This is a condition manifesting itself in middle aged individuals. Sclerosis of the arteries supplying blood to the corpus striatum and closely related structures, is taken to be the causative factor. It is also known as senile Parkinsonism. The cardinal features are rigidity, tremors and absence or poverty of associated movements.

Rigidity — Marked hypertonus of all groups of muscles, in a nonselective way, is a prominent symptom. The individual assumes a statuesque attitude, and there is no expression on the face which is said to be mask-like and devoid of emotion on account of the facial muscles becoming immobile. The increased muscular tone is a reflex effect and is reduced or abolished by de-afferentation of the muscles just like decerebrate rigidity. The deep reflexes are however, not brisk or exaggerated. Jendrassik's manoeuvre does not reinforce the knee jerk. There is also no actual paralysis of muscles. One consequence of the greater tone of muscles is that the gait is altered and it becomes shuffling with short steps. It is known as the festinant gait. The subject has a bent attitude while walking. This has been picturesquely described as an attempt at catching the centre of gravity. When a push is given, the affected person is not able to stop himself in time and continues to move either forwards or backwards in the direction of the push and is

compelled to take short and quick steps. Propulsion and retraction are terms used in this regard. The structures implicated are the globus pallidus and the substantia nigra.

Abnormal movements: Tremors or fine rhythmical involuntary movements (tremors at rest or static tremors) occur in the distal joints of the limb, especially the digits of the hands. These persist throughout the wakeful period. Volitional movements reduce their severity or abolish them. Sleep also causes their disappearance. The probable underlying basis for tremors has been referred to above. Another type of abnormal movement which is seen in this condition, is "pill rolling" movements of the fingers.

Absence of associated movements: The swinging of arms normally noticed while walking, is an associated movement. This as well as other associated movements, are absent in Parkinson's disease. Poverty of movement is the phrase denoting the paucity of such movements.

Sometimes, Parkinsonism may occur in young adults who have been exposed to virus infections like influenza or encephalitis. Symptomatology is similar to that of the senile condition.

Chorea means rapid jerky semi-purposeful movements, seen especially in the arms and face. Like tremors, these are seen at rest. Contortions of the face (grimacing) are also observed. The jerky movements disappear during sleep. The putamen and the caudate nucleus are held to be the seat of damage responsible for chorea. Two kinds of chorea have been described, based on aetiology. In Sydenham's chorea (St. Vitus' Dance), a bout of rheumatic fever seems to be the predisposing cause. The other form is Huntington's chorea which is a familial condition and is inherited through a dominant gene.

Hemichorea or hemiballismus is attributed to lesions in the subthalamic body of Luys. This is limited to one half of the body and is manifested as wild flinging movements of the limbs. Interrupting the corticospinal pathways at any convenient level is a method of suppressing the abnormal movements.

Athetosis is characterised by sinuous, wormlike movements of the limbs simulating the gestures of oriental dancing. This condition may reveal itself even in childhood. The same nuclear masses as in the case of chorea — putamen and caudate nucleus may be at fault, in this condition also. It may sometimes be present along with chorea.

Torsion spasm is yet another manifestation of diseases of basal ganglia. Twisting and turning of the trunk and extremities and distorting the body into abnormal postures, are the visible symptoms. Widely dispersed lesions of basal ganglia may be responsible.

Wilson's disease or hepatolenticular degeneration: The underlying pathology is due to a disordered copper metabolism. Cirrhosis of liver may be an associated condition.

THE CEREBELLUM

This is a part of the hind brain or rhombencephalon. It is made up of three easily distinguishable anatomical divisions (fig. 60)—the central vermis which is bent upon itself and the two

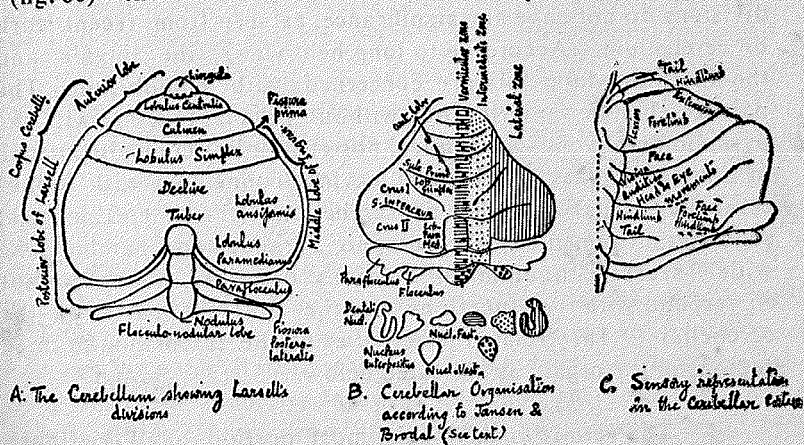


Fig. 60.

(A)—After Dow, R. S., J. Neurophysiol., Vol. 5, p. 121, 1942.

(B)—After Jansen and Brodal, Avh, norske VidenskAkad., KI, 1942, No. 3.

(C)—After Dow, R. S., Biol. Rev., Vol. 17, p. 179, 1942.

cerebellar hemispheres which have attained the maximum development in primates — these two components form the corpus cerebelli. The flocculonodular lobe which is separated from the corpus cerebelli by the fissura posterolateralis is phylogenetically the oldest part and hence is known as the archicerebellum. The fissura prima in the corpus cerebelli demarcates the anterior lobe (anatomical) from the posterior lobe. The different regions of the vermis are given various names as follows — Anterior most is the lingula and in order, there are lobulus centralis, culmen and lobulus simplex. The functional anterior lobe extends behind the fissura prima to include the lobulus simplex also. Next there are — the declive, tuber, pyramid, uvule and the nodulus. The lateral enlargement on each side of the vermis — the cerebellar hemisphere comprises the lobulus ansiformis anteriorly and lobulus paramedianus posteriorly (tonsil). The fissura prepyramidalis in the posterior part of the corpus cerebelli causes a further division of the anatomical posterior lobe into a middle part (middle lobe of Ingvar) and a posterior part.

From the functional point of view, the above mentioned divisions do not have any significance, as seen from recent work on cerebellum. According to long held views, the lingula and the flocculonodular lobe are concerned with equilibrium. The paleocerebellum (anterior lobe without lingula, together with the pyramid and uvula — anatomical posterior lobe) controls the tone of muscles (spinal cerebellum having connection with spino-cerebellar tracts) and the neocerebellum (the lateral masses) regulates movements. According to Sprague and Chambers, the widely accepted anatomical divisions described above do not correspond with the functions of the different parts of the cerebellum. They relate the activities of the cerebellum to three regions of the organ, as indicated below.

1. The vermis or the medial most portion of all the lobes of the cerebellum including that of the flocculonodular lobe — Maintenance of equilibrium.
2. The paravermal regions, a narrow zone of cerebellar tissue on either side of the vermis — Regulation of tone of muscles.

3. The *lateral* most areas on either side — control of movements.

The cellular structure of the cerebellum:— the cerebellar cortex covers the inner core of white matter which in a sagittal section resembles a tree and hence called arbor vitae. The grey matter of the cortex is thrown into transverse folds by fine sulci and the elevations of grey matter which run from side to side are called folia (leaves). The grey matter or cortex presents the same cellular structure throughout, unlike the cerebral cortex. Three well differentiated zones are seen and these are, from without inwards:

1. Molecular layer consisting of unmyelinated fibres arborising around the Purkinje cell dendrons and small star-shaped cells situated superficially and large stellate cells (basket cells) deeper, with their axons running parallel to the external surface and coming into synaptic contact with a large number of Purkinje cells, by means of collaterals.

2. Layer of Purkinje cells — These are flask-shaped cells peculiar to the cerebellum. They have their axons entering the white matter to synapse with the cells of the cerebellar nuclei. Their dendrons show tree like ramifications, the branches and the twigs all confined to a single plane like ivy (a creeper) on a wall

3. The granular cell layer of small, round and closely packed cells: The axons enter the molecular layer and connect up with the dendrites of several Purkinje cells. Moss fibres bring impulses from extra cerebellar regions to these cells. Even the fibre connections of the cerebellum can be described with reference to the divisions mentioned above (See below). The incoming and the outgoing fibres of the cerebellum are funnelled through the three pairs of cerebellar peduncles. The inferior cerebellar peduncle (restiform body—mainly afferent) conveys most of the afferent fibres of cerebellum — viz — the dorsal spinocerebellar tract, olivocerebellar tract, vestibulo cerebellar pathway, as well as the dorsal external arcuate fibres relayed from the cuneate and gracile nuclei of medulla. The efferent fibres passing through this structure will be those that make contact with the vestibular nucleus, inferior olivary body and the reticular formation of the brain stem. The middle peduncle (brachium pontis) is composed of the fibres arising from the pontine nuclei of the opposite side to provide

linkage of the cerebrum with the cerebellum and the commissural fibres from the opposite half of cerebellum. The superior peduncle (brachium conjunctivum – mainly efferent) provides passage for the afferent fibres of the ventral spinocerebellar tract and the efferent fibres from the dentate nucleus to the contralateral red nucleus and thence to the lateroventral nucleus of the thalamus to be ultimately relayed to the motor areas of the cerebral cortex of opposite side. The reticular formation of the midbrain, thalamus and hypothalamus also receives fibres from the cerebellum. The tectum of midbrain sends fibres to the cerebellar cortex.

The afferent fibres to the cerebellum belong to two categories.

1. The moss fibres which are the terminations of the spinocerebellar and olivocerebellar tracts. They end in the innermost layer of the cerebellar cortex, forming synapses with the granular cells and through them they activate the purkinje cells.
2. The climbing fibres are the afferents from the vestibular and pontine nuclei and these pass into the outermost molecular layer of the cortex where they establish contacts with several purkinje cells.

The cerebellar nuclei: On each side there are four nuclei or masses of grey matter in the core of the cerebellum. These receive the axons of the purkinje cells and their projections leave the cerebellum for the various parts of the brain through the cerebellar peduncles.

The cortex of the vermicular zone sends fibres to the Nucleus Fastigii (roof nucleus, most medial of the cerebellar nuclei). The intermediate or paravermicular zone gives off fibres to the nucleus globosus and emboliformis. The lateral lobe makes connections with the dentate nucleus which is the most lateral of the four nuclei. This is phylogenetically a recent acquisition and it, in a section, looks like a zig zag band folded on itself.

The afferent and efferent connections of the cerebellum can be summarised as follows :

	Afferent fibres from	Efferent connections with	Nucleus for relaying efferent fibres.
Vermicular zone	Vestibular nucleus, Collaterals	Vestibular nucleus	Nucleus Fastigii(2 is)

	of sensory tracts, Spinocerebellar tracts.	Reticular formation of brain stem.	
	Inferior olive, Afferents from 5th cranial nerve.	Inferior olive	
Intermediate zone	Collaterals of sensory tracts.	Midbrain Reticular formation Thalamus and Red Nucleus.	Nucleus emboliformis nucleus and globus.
Lateral zone	Cerebral cortex of opposite side, Upper brain stem through inferior olive.	Opposite cerebral cortex (areas 4 & 6) through red nucleus & thalamus.	Nucleus dentatus

It has to be noted that the cerebellar half of one side controls the muscles of the same side since it sends impulses to and receives impulses from the motor areas of the cerebrum of the opposite side. The cerebellar activities are carried out beneath the level of consciousness.

Experimental Studies on Cerebellar Function: Luciani performed ablation of the cerebellum in animals and described three stages in the development of symptoms.

1. Functional exaltation: There was increase in the tone of muscles and clonic movements occurred and the body assumed a posture with back arched with neck and limbs extended. This was considered to be a release phenomenon.

2. After about a week, muscular weakness (asthenia) supervened, accompanied by ataxia (incoordination) and atonia. These three symptoms form Luciani's triad and this stage was called by him as one of *maximum cerebellar deficiency*.

3. Stage of compensation—deficiency symptoms disappeared due to compensation by area 6 of the cortex. Removal of this area of cortex prevented compensatory changes. If area 4 is now

removed, the symptoms of cerebellar deficiency become less marked.

Unilateral ablation of cerebellum—the effects are seen on the same side of the body as the half removed.

Results of lobewise removal: a) with loss of Flocculonodular lobe disturbances in equilibrium resulted.

b) with loss of spinal cerebellum (anterior lobe) tone and posture affected.

c) with loss of neocerebellum (posterior lobe) incoordination of muscles in voluntary movements.

Section of peduncles :

Total section of all peduncles — same effect as total ablation of cerebellum.

Section of inferior peduncles — disturbance of equilibrium.

Section of superior peduncles — tone and movements mainly affected.

Section of middle peduncles — no definite symptoms.

When all the peduncles of one side are interrupted giving rise to the same effects as ablation of the cerebellum of one side, the remaining half will be instrumental in compensating for the loss. The frontal lobe also is partly responsible for this.

Stimulation of cerebellar nuclei - When the dentate nucleus of one side was stimulated with faradic current, the tone of ipsilateral limb flexors was increased with diminution of that of extensors. The tone of trunk muscles on the stimulated side was also increased causing curvature of the body towards that side. On stopping the stimulation, rebound effects were seen. More pronounced effects of the same nature were elicited by excitation of the nucleus globosus and nucleus emboliformis. Stimulation of the fastigial nucleus caused strong flexion of both the forelimbs.

Localisation in cerebellar cortex: Collaterals from all the sensory pathways seem to reach the cerebellar cortex, as evidenced by the recording of activity set up in the cerebellar cortex by impulses coursing up any of the ascending pathways. There exists a topological representation of the body surface, the retina and the cochlea. All the sensory modalities are represented in the cerebellum. There is actually a duplication in this. The face

(vibrissae), the forelimb, the hind limb and the tail of a cat have areas devoted to them, in order, in the lobulus simplex, culmen, lobulus centralis and lingula, respectively. The posterior lobe exhibits a similar representation but in the reverse order, the face area anteriormost and the tail hindmost. It has also been observed that the anterior lobe has reciprocal connections with the somaesthetic area I in the post central gyrus of the cerebrum, while the posterior lobe is linked with the second sensory area of the cerebral cortex. Even visual and auditory impulses evoke activity in the cerebellar cortex—from lingula to as far posterior as the lobulus ansiformis. The superior and inferior corpora quadrigemina relay fibres to the cerebellum from the visual and auditory pathways, respectively.

The motor cortex (area 4) has systematic to and fro connections with the cerebellar cortex where in the representation for the muscles coincides with those for sensations. While actual movements may not arise out of stimulation of these areas, facilitation or inhibition of motor activity is a consequence.

FUNCTIONS OF THE CEREBELLUM

Equilibrium: Early studies by Dow, following ablation of the flocculonodular lobe in the monkey, showed 'disequilibrium'. The animal was not able to stand without support. It went into a corner of the cage and supported itself by the two walls meeting at the corner. There was no paralysis of muscles. It could put out its hand for titbits. There was no sensory loss either. This role of the flocculonodular lobe, as shown by work in the recent past, should be rightly ascribed to the vermal region of the entire cerebellum including the nodulus. Removal of the nodulus in the dog rendered the animal immune to motion sickness. The reciprocal connections between the vestibular nucleus and the cerebellum provide the anatomical basis for this function. In fact, during the course of evolution, the cerebellum has developed from the vestibular nucleus. It is for this reason and its being linked with the spinocerebellar tracts, that Sherrington considered the cerebellum as the head ganglion of the proprioceptive system. Now it is realised that it is more than merely the head ganglion. Lesions placed in the anterior vermal portion produced the same effect of loss of equilibrium. This is

due to the fact that the vermis has to and fro links with the nucleus fastigii (see above). The anterior part also receives fibres of the spinocerebellar tracts, conveying 'non-sensory' impulses from proprioceptors and tactile end organs. Visual and auditory impulses also find their way to the medial part of the cerebellum. Thus, the rich sensory input to the vermis enables it to subserve the maintenance of equilibrium.

Adjustment of muscular tone: Stretch reflexes underlying postural mechanisms seem to be under the control of the cerebellum. In a classical decerebrate preparation (cat), cooling or ablation of the medial anterior lobe enhances the tone of the antigravity muscles (mostly extensors), while stimulation minimises the rigidity of these muscles. In man, a pathological lesion of the medial part of the anterior lobe did not however, release the extensor (antigravity muscle) stretch reflex. In animals, Sprague and Chambers observed that destruction of the fastigial nucleus of one side caused rise in extensor tone of the opposite side but fall in flexor tone of the same side. On the contrary, ablation or destruction of the vermal cortex produced opposite changes. Hence it follows that the vermal cortex normally inhibits the fastigial nucleus whose function is to reduce the tone of contralateral extensors but raise ipsilateral flexor tone. Further, while stimulation of the vermal cortex of anterior lobe reduces the tone of antigravity muscles (by reducing spindle afferent discharge), in a classical decerebrate preparation, excitation of the paravermal region of the same lobe raised the tone of these antigravity muscles.

Hypotonia is a prominent symptom of cerebellar disease in humans. Removal of the lateral lobes in the primates caused hypotonia. The cerebral cortex receives impulses from the lateral lobes through the efferent fibres (of the dentate nucleus) which are relayed by the red nucleus and the thalamus. The facilitatory effect of the pyramidal tract on the extensor stretch reflexes is sustained by the barrage of afferent impulses from the cerebellar lateral lobes. When these are the site of injury, hypotonia will follow as a corollary. In addition, by virtue of its connections with the red nucleus, the cerebellum (lateral lobes) may act through either the rubrospinal tract or by the descending facilitatory reticular system and thereby maintain the tone of muscles

at a high level. Hypotonia in cerebellar disease may be due to the absence of this facilitatory action through the reticular formation. On the other hand, the medial portions of cerebellum seem to be inhibitory to the extensors. Hypotonia in cerebellar disease must be mainly due to lesions of the lateral lobes.

Control of voluntary movements: This control relates to the rate, range, force and direction of movements. The lateral and paravermal regions, by means of their connections, are most probably implicated in this. The dexterity of voluntary movements exhibited by the primates, in which the lateral lobes have attained the greatest development, seem to indicate such a function. Lesions of dentate nucleus have produced marked interference with voluntary movements. But, since the paravermal zone exhibits a high degree of organisation, it seems to be even more concerned in this cerebellar function. Ataxia or incoordination has been observed as a result of injury to the paravermal region.

Clinical manifestations of cerebellar disease: Medulloblastomas seen in children, give rise to symptoms like those resulting from the lesions of flocculonodular lobe, as observed by Dow in monkeys. The gait and posture are affected (staggering or reeling gait) without disturbance in tone of muscles, especially when the anterior vermis only is involved. Usually, however, the symptoms arise out of involvement of large areas of cerebellum. Pendular knee jerk is a feature attributed to the failure of the antagonistic knee flexors to respond to stretch reflex, as the knee is hyper-extended. Hypotonia of muscles is also a concomitant occurrence. The most prominent effects are seen in relation to voluntary movements. Incoordination is the hall mark of cerebellar disease. Muscular weakness (asthenia—too little force), lack of precision in the extent of movement (dysmetria), unsteadiness (tremor) constitute the symptom complex. Past-pointing is a result of this. Adiadokinesis or inability to rapidly perform alternating movements like pronation and supination of the forearm, reflects the inability to start and stop movements promptly. Tremors which become aggravated towards the end of a volitional movement (terminal or intentional tremors), distinguish cerebellar disease from Parkinsonism. Dysmetria is the cause of this ataxia and

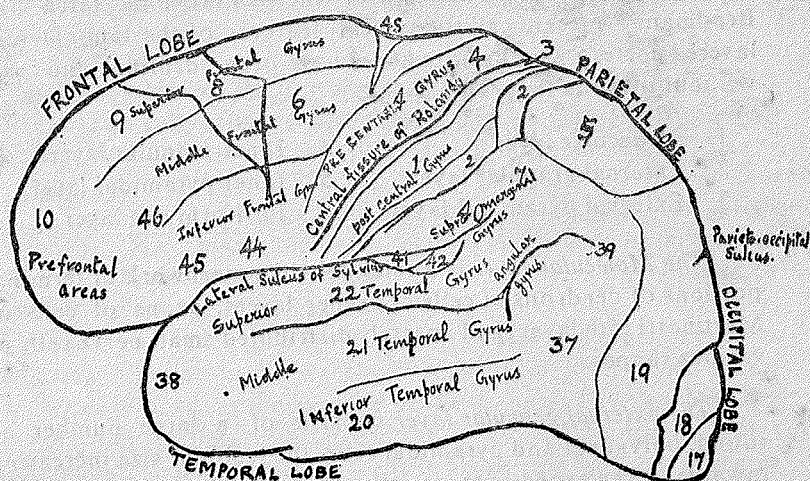
tremor. The cerebrum is deprived of the feedback from the cerebellum to regulate the range and force of voluntary movement. Over-correction and under-correction bring about uncertainty towards the terminal stages of voluntary movements. Vertigo, nystagmus and arching over of the body to the side of lesion are additional symptoms. The symptoms are confined to the same side of the body as the lesions in the cerebellum.

To sum up, for accurate control of volitional movements, the cerebral cortex must receive an input of impulses duly processed from the cerebellum which receives signals from a wide range of receptors. Thus, the cerebellum furnishes an accurate feedback control for the motor activity initiated from the cerebral cortex.

THE CEREBRAL CORTEX

The grey mantle or the cortex of the cerebral hemisphere is so called because of its darker appearance compared with the white matter. In the human brain, it has an extent of about 220,000 sq. mm. of which only a third is seen externally, the rest being buried in the sulci or fissures. The number of nerve cells forming the grey matter is a very large figure, estimated to be around 7×10^9 which is fixed at birth. The study of the arrangement of the cellular and nerve fibre elements in the cortex, has been termed fancifully and a little pretentiously, as Cytoarchitectonics. Several workers interested themselves in these investigations, notable among whom were Campbell, the Vogts and Brodmann. They divided the entire cerebral cortex into many zones (each denoted by a number) based on the preponderance of a particular cellular arrangement in each. The number of such demarcated zones varies from author to author; that of Brodmann has secured widest acceptance. He marked out 47 areas on the cortical surfaces (fig. 61), both medial and superolateral. Some definite functions have been assigned to some of these numbered areas, while the possible functions of many of them are still to be elucidated. In parenthesis, it may be stated that eventually it may be found to be impossible to strictly assign a function to each and every cortical area however attractive such a culmination might have appeared in the past.

A. Cerebral hemisphere - Supero-lateral aspect



B. Cerebral hemisphere - Medial aspect

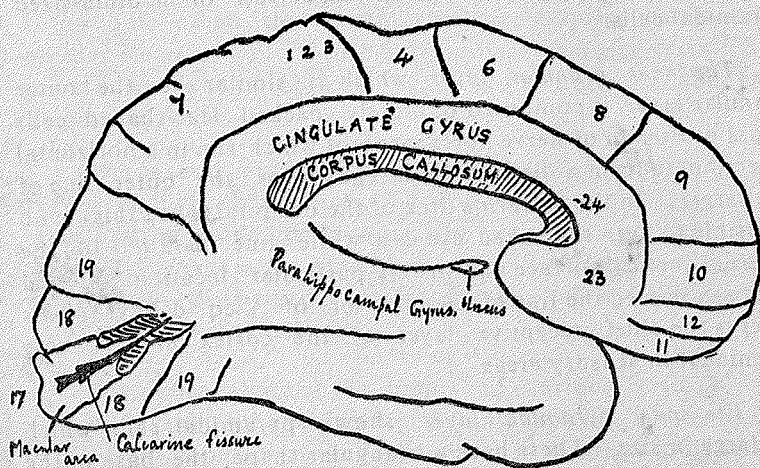


Fig. 61.

Detailed structural studies have shown that about 1/12th of the entire cortical area which is phylogenetically old and hence

called archipallium, is not highly organised as the rest of the cortex which exhibits a laminated structure (Neocortex, neopallium or isocortex). The motor area of the frontal lobe (area 4 of Brodmann) presents all the typical features of the laminated or layered cortex. Six definite zones have been identified and from without inwards they are :

- | | |
|------------------------------|---------------------------|
| 1. Molecular layer. | 4. Inner granular layer. |
| 2. External granular layer. | 5. Inner pyramidal layer. |
| 3. External pyramidal layer. | 6. Fusiform cell layer. |

The Molecular layer is a thick felt-like meshwork of terminal portions of dendrons of cells of deeper layers, axons of cells of Martinotti (5th layer) and sparsely distributed small nerve cells of various shapes.

The external granular layer consists of a large number of round, polygonal and pyramidal cells, the cellular size increasing inwards. The axons of these cells enter the deeper layers, while their dendrites can be found in the molecular layer.

The external pyramidal layer is made up of medium-sized pyramidal cells.

The inner granular layer which is similar to the outer granular layer, is composed of closely packed star-shaped cells and a profusion of nerve fibres many of which run in a horizontal direction, to form a distinct band known as the outer line of Baillarger. In the calcarine area of the occipital lobe, this band is visible to even the naked eye as a white line parallel to the external cortical surface and in this particular location only, it has been named the line of Gennari or of Vicq d'Azyr. This layer is the chief receptive layer of the cortex and is very prominent in sensory areas.

The inner pyramidal layer shows pyramidal cells which are large in size. These have a triangular shape, the base of the triangle giving rise to the axon which penetrates the white matter and the apical portion giving off numerous dendrites seen in more superficial layers. The unique cells of Martinotti which are found in this layer, send their axons not into the white matter but towards the molecular layer. The large pyramidal cells of

Betz (length upto 90μ and greatest width at base upto 80μ) are seen only in the area Gigantopyramidalis, occupying the anterior lip of the central fissure of Rolando and the posterior part of the precentral gyrus.

The innermost, the fusiform cell layer, presents spindle-shaped or fusiform cells oriented with their long axes at right angles to the cortical surface. Other types of cells are also present.

The laminated cortex showing the typical layering is called homotypical cortex, while other regions of the neocortex, because of the unbalanced prominence of some layers in contrast to others, have come to be known as heterotypical cortex. Further, cortical areas which give rise to motor effects (muscular contraction) on stimulation, have the pyramidal layer, outer and inner, better developed at the expense of the granular layers. Sensory areas which are receptive in function, have their granular layers prominent. Since pyramidal cells in these are not conspicuous due to their smaller size and smaller numbers, sensory areas present a dusty appearance in histological preparations and the term Koniocortex has been applied to these areas of the cortex. It has to be noted that histological techniques which reveal cellular elements will obscure fibre systems and vice versa. So it is not possible to see both cells and nerve fibres in the same preparation.

Over several centuries, a large number of workers interested themselves in the elucidation of brain functions using more and more refined modes of investigation as years went by. While considerable advances have been made, yet there is still much more to be discovered. Some of the well known methods employed are listed below.

1. Anatomical study of the brains of various animals. The phylogeny of the parts of the brain was studied — especially the development of the forebrain in primates and the attenuation of the smell brain in higher animals.
2. Embryological method — The development of the various tracts and the stages of myelination were taken note of. In general, sensory pathways are myelinated at birth but the motor tracts are fully myelinated subsequently only.

3. **Ablation of parts of the brain and observation of the consequent defects.** Though much was expected of these studies, it has become apparent that the effects of such drastic procedures brought on complications due to incidental damage to other parts of the brain and thus, it was not possible to distinguish the direct effects of such ablations per se. Even electrocoagulation, as is used in modern work, involves injury to nearby parts of the brain. Compensation for the loss of one lobe or part thereof by the remaining parts of the brain, brings in complications and vitiates inferences which are drawn.
4. **Electrophysiological procedures:**
 - a) **Stimulation** — The results of stimulation of cortical regions have been codified. Certain areas have been recognised to be motor in function, since muscle contraction resulted on stimulation. Even 'purely' sensory areas gave rise to weak motor activity on stimulation, though, sensations referred to various parts of the body depending on the point stimulated, were the predominant effects. Pain, however, was never caused. Some parts yielded no visible effect and in the early days were named as 'silent' areas, though this concept has now undergone a revision.
 - b) **Evoked potentials** — when peripheral parts of the body were stimulated with natural stimuli, action potentials could be recorded in the so-called sensory areas. This led to the mapping out of the homunculi by Penfield and others in man and simunculi, in the ape or monkey by Woolsey and others.
 - c) **Strychnine Neuronography (Physiological neuronography):** The application of very tiny pieces of blotting or filter paper soaked in strychnine solution, to the cortical surface, sets up electrical activity in other parts of the cerebral cortex or in the subcortical structures. A highly organised and complicated system of inter-connections among the different parts of the brain has been revealed by this means. Not only excitatory but also depressant actions of the one area in the brain over the others, have been observed. The discovery of the so-called 'suppressor areas' of the cerebral cortex followed from this type of study.

In the following account of the possible functions of the cerebral cortex, the hemisphere is considered lobe-wise—the

fourfold division into Frontal, Parietal, Temporal and Occipital lobes, being based on well-recognised anatomical boundaries.

Frontal lobe : The anterior-most part of the cerebral hemisphere, lying in front of central sulcus of Rolando, contains the motor areas 4, 6, 8 and 4S in addition to the prefrontal areas 9, 10, 11, 12, 13, 24 and 44. The motor area 4 occupies the anterior lip of the central fissure and the visible part of the precentral gyrus in addition to an area on the medial surface of the hemisphere in continuation with the precentral gyrus. Stimulation with faradic current, of points in this area, causes contraction of a part of a muscle, a whole muscle or even a small group of muscles, resulting in a discrete movement of a joint but not a well-organised one in which synergists also take part. Since muscle contraction or motor effects are obtained from this area, it has come to be known as the primary motor area. Thus, it is said that muscles are represented in the area 4 but not movements. Which muscles are activated will depend on which part of the area 4 is excited. It has been found by Penfield and others, in man — in conscious human subjects during brain operations, and by Wolsey and others, in monkey and ape, that relatively large areas in the precentral gyrus are devoted to motivating those muscles in the body which can execute very precise and delicate movements like those of digits of the hand and tongue. Thus, the distal parts of the limbs have portions of greater extent devoted to them than the proximal parts and further, the digits are apportioned much larger areas, compared to the rest of the limb. Similarly, lips and the tongue have more area assigned to them than the rest of the face. The mapping out of the areas has yielded Homunculi (man) and Simunculi (monkey and ape) which are highly distorted versions of the human and simian figures. The homunculus shows the body in the inverted position, the face and head occupying the lowest part of the precentral gyrus, followed by the neck, the thorax and abdomen in the upward direction. The digits of the forelimb are situated posterior to the thoracic region but have disproportionately large areas meant for each one of them. The thumb area is much greater in comparison with those of other digits. In the case of hind limb, the thigh is represented in the superior-most portion of the precentral gyrus, the knee region at the

superior free margin of the hemisphere, the lower leg with the feet and toes represented on the medial surface. The homunculus, so to say, hangs upside down with the leg hooked over the superior border of the hemisphere. The face region, however, does not conform to the inverted 'position', of the body it being represented in the normal erect position though with great distortion, the tongue and lips very much magnified and out of proportion to the rest of the face. It must be mentioned however, that there is no constancy of responses that can be elicited by stimulation of any one point. If an extension of a joint occurs at one time, flexion may occur at another time. Frequently, stimulation of some point may bring about the movement of a joint, not elicited from it before. Thus there is a great variability in the responses, even though there is basically a spatial representation of various muscles and muscle groups of the body. Faradisation over long periods may even produce convulsions simulating epilepsy. The trunk area in general, occupies the anterior region and those of the limbs are relegated to posterior parts of the gyrus. In addition to movements of the contra-lateral muscles, those of bilaterally innervated structures like jaw, vocal cords and the external anal sphincter, can also be evoked by stimulation of motor area on one side. Strangely however, when brief pulses of direct current are employed to excite the different points of the motor area, a stereotyped response is obtained, composed of movements of the thumb and the index finger, the big toe and that of the angle of the mouth of the opposite side. This is so, whichever part of the motor area is subjected to stimulation. In this connection, the observation of Hughlings Jackson that epileptic fits commence nearly always in the hand or foot or in the angle of the mouth, is of significance. A secondary motor area has been shown to exist and it occupies a region below the prefrontal gyrus and in continuation with it. The body is represented in the erect manner in this area and even more significantly, the face region of the same side is well represented here. Consequently, facial muscles are not paralysed in unilateral cortical or capsular lesions. The implication of the existence of a second motor area has not yet been understood. A third area known as the supplementary motor area is located on the medial cortical surface lying immediately anterior to the leg and foot regions of the primary motor area. The threshold for stimulation is higher

in this area than in the primary motor area. Purposeful acts like yawning, crying and coordinated movements of head and eyes can be elicited by stimulation of this area, in the anaesthetised animal. In the conscious human subject, bilateral movements can be evoked. The movements provoked resemble the assumption and holding on to a particular posture of the limb, rather than those of a transient or phasic nature. Intimate interconnections exist between the motor and premotor areas of one side and also the supplementary area, though the motor area can act independently of the other areas. No contribution to the pyramidal tract arises from the supplementary area.

Area 6: Premotor area — This region is separated from area 4 by the wedge-shaped suppressor area of Hines (4S). Excitation of the premotor area (6) results in well coordinated and purposeful movements of joints in the opposite half of the body. The effects involve agonists or the prime movers, in addition to synergists and have a longer latency than in the case of the motor area proper. They build up in intensity more gradually and outlast the duration of stimulation. Such movements are termed 'holokinesis' while those elicited from area 4 are known as Idiokinesis. Interruption of the connections between the premotor and motor areas abolishes the holokinetic type of movement, implying that these effects are mediated by the area 4. Even eye movements can be elicited from the superior portions of this area. Vasomotor effects can also result from stimulation in this region.

4S Suppressor area of Hines: The motor effects elicited from area 4 can be suppressed by simultaneous stimulation of the area 4S. This effect seems to be brought about through its connection with the caudate nucleus which inhibits the area 4. Excision of this area causes a rise in tone of muscles. Some doubt has arisen as to whether such suppressor areas located in well-defined regions exist.

Area 8: This region is also known as frontal eye field, and conjugate adverse movement of the eyes and head can be elicited by stimulation here. Even lachrymation and pupillo-dilatation can be effected. The neurones of this region provide cortical control over eye movements.

Effect of ablation of areas 4 and 6: After removal of area 4, stimulation of area 6 will bring about inhibition of motor activity. Removal of area 4 alone, in the ape or man, will cause flaccid paralysis and loss of deep reflexes, both on the opposite side. In monkey however, such an operation will not cause loss of memory for movements already learnt and for which training can be given once again. In ape and man however, even though movements can be re-established to a large extent by patient training, yet manipulative dexterity in the performance of voluntary acts is never fully regained. The plantar response in humans will consist of dorsiflexion of the great toe without any movement of other toes. Removal of area 6 on the other hand, will bring about hyper-tonus of muscles on the opposite side, exaggerated deep reflexes and only fanning out of the toes without affecting the great toe at all. Involuntary forced grasping and groping movements may be seen.

Forced grasping and groping movements: When the intervening region (of the hand) between the thumb and forefinger is touched with a slender object like a pencil, these digits tend to curl round it. Withdrawal of the pencil gently without disturbing the position of the hand, will cause the hand to follow the object in the manner of a piece of iron attracted by a magnet. This is the groping reflex. When the object is allowed to be held by the curling of the fingers, if it is attempted to be pulled away, the hand grasps it with more firmness. Also, passive movements of limbs will meet with resistance throughout the extent of the movement (lead pipe rigidity) unlike in clasp knife type of rigidity. The gentle grasp giving rise to the groping movement is voluntary and can be avoided at will. The strong grasp evoked by withdrawal of the held object and the lead pipe spasticity, are due to a stretch reflex of the muscles involved. Autonomic disturbances are associated features in this condition. There is loss of memory for complex movements and the individual animal (ape or monkey) or man cannot be trained to perform movements which were very familiar before the operation. There is thus a loss of memory for patterns of learned movements. Rossolimo's sign can be elicited—flexion of toes will occur when they are flicked on their plantar surfaces. Unilateral removal of areas 4 and 6 together, will produce

symptoms identical with that of a clinical hemiplegia on the opposite side. Section of the pyramid in the medulla causes effects similar to those of loss of area 4. Removal of area 6 after pyramidal section, brings about increased extensor tone on the opposite side. Stimulation of area 4 now, will abolish extensor tone both on the affected side as well as on the other side. Stimulation of area 6 brings about diminution of flexor tone with loss of grasp reflex.

Areas 4, 4S & 6, by virtue of their connections with extrapyramidal system, regulate movements brought about through the activation of area 4 or the pyramidal tract itself. Area 4S & 6 inhibit flexor tone but area 4 suppresses extensor tone. The premotor area 6 is necessary for learning skilled movements

A lesion of the internal capsule which produces the classical syndrome of hemiplegia of the opposite side involves damage to both pyramidal and extrapyramidal fibres. Clinically, it may not be possible to see lesions purely of area 4 or of area 6.

Pre-motor syndrome : A lesion affecting area 6 mainly, sometimes seen clinically, will have the following features –

- 1) Awkwardness in performing skilled movements but no appreciable loss of power for gross movements.
- 2) Spasticity of muscles with increased vigour of tendon reflexes.
- 3) Increased grasping and groping movements.
- 4) Autonomic disturbances.

Area 44 : This is well known as Broca's area and lies in the inferior frontal convolution in front of the lowest part of the precentral gyrus, in the dominant hemisphere (left usually). Broca found lesions of this area in certain cases of speech loss and hence called it the speech area or glossokinaesthetic area. Stimulation of this area in conscious subjects however, caused arrest of speech.

The prefrontal areas 9, 10, 11, 12, 13 & 24 : These lie at the anterior extremity of the hemisphere, on the anterolateral and medial aspects and also on the orbital surface. No recordable or

observable responses were obtained in early studies and so these areas were considered to be inexcitable and came to be known as silent areas. Later however, with refined methods of stimulation, certain autonomic effects were observed in the form of alterations in heart rate, blood pressure and such like, from area 13 on the orbital surface.

The prefrontal areas receive fibres mainly from the thalamus and the hypothalamus. The dorsomedial nucleus of the thalamus gives off fibres to areas 8, 9, 10, 11 & 12 as well as areas 44-47. This nucleus in its turn is connected with the posterior hypothalamus by afferent fibres. The anterior thalamic nucleus which receives connections from the mammillary bodies, provides afferent fibres to reach the area 24 in the cingulate gyrus which is a 'suppressor' area. On the efferent side, fibres are returned to the thalamus and the hypothalamus, even directly. The anterior, medial and intralaminar nuclei of the thalamus have reciprocal connections with prefrontal areas. This closed circuit is held to be responsible for the electroencephalogram, at rest. The occipital and temporal lobes derive association fibres from the prefrontal areas. The caudate nucleus, the mammillary bodies and the tegmentum of the midbrain receive fibres from the prefrontal areas.

Functions of the prefrontal lobe: These may be related to the personality of the individual, emotional responses and behaviour. The effects of the ablation of the prefrontal areas are not quite apparent. They can be revealed only by a very close examination of the subject. Such an operation was performed at first by Egas Moniz, a Portuguese surgeon, in certain cases of mental illness. This operation produces the following effects:

- 1) An attitude of cheerfulness resembling euphoria or a false sense of well being.
- 2) Lack of self introspection or criticism, leading to boastful speech.
- 3) A mind easily distracted and unable to concentrate even on simple problems.
- 4) Inability to take even minor decisions and to plan a course of action even in trivial matters.

- 5) In certain cases of aggressive psychosis, improvement has been seen.
- 6) Intractable pain can be relieved without lowering intellectual capacity by sectioning subcortical connections. Perception of pain is not abolished though its affectivity or unpleasantness is diminished and the patient ceases to worry about it.

In animals like the monkey, the following results have been observed after prefrontal leucotomy.

- 1) Loss of activity as evidenced by an apathetic attitude which occurs in the initial stage. This changes to one of hyperactivity, subsequently, the animal becoming restless, pacing to and fro like a caged animal, in an aimless manner. Loss of area 13 may be the cause of this symptom.
 - 2) Temper tantrums brought about by mental confusion in choosing suitable test objects for obtaining rewards, become very much mitigated or abolished by ablation of area 24. Lesions in areas 13 & 14 on the other hand, produced a sham rage-like state.
 - 3) Loss of area 24 abolished the fear response. A monkey which underwent such an operation, fearlessly handled snakes of which it was normally mortally afraid. It approached man without shyness. It took away food from its companions, ignoring their need. A blunting of social conscience is a characteristic effect.
 - 4) Loss of memory leading on to failure or extinction of learned responses or conditioned reflexes; also, an inability to learn new tricks is an associated feature.
- The original operation of frontal lobectomy has yielded place to newer operations like pre-frontal leucotomy (cutting the white matter only), pre-frontal topectomy (excision of grey matter), pre-frontal lobotomy (mere sectioning of the hemisphere posterior to the prefrontal lobe but not removal altogether)

The prominence of the frontal lobes in the primates, especially in man, led to the notion that they may be the seat of intelligence. Clinical studies involving surgery for pathological lesions in the prefrontal lobes, resulted in false conclusions being

drawn. Careful studies of war injuries in this part of the brain, based on objective tests, revealed no intellectual deficits in these cases. Thus, it does not appear sound to attribute intelligence to the greater development of the prefrontal areas. The view is gaining acceptance that the parietal lobes may be more intimately concerned with the development of the intellect. Prefrontal lobes, by virtue of their connections, seem to be responsible for the emotional make up of the individual, initiative for action and judgement in choosing between courses of action. It is safer to consider higher intelligence as the total effect of the functions of the cortex as a whole.

The Parietal lobe : This is bounded posteriorly by the sulcus occipitoparietalis and inferolaterally by the sylvian fissure. The physiologically important centres in this part of the cerebrum are Brodmann's areas 3, 1, 2, 5 & 7, all of which are on the lateral surface. The main function of this lobe is related to sensations. In the post central gyrus are situated areas 3, 1 & 2, each occupying a narrow strip of this gyrus and disposed one behind the other in the order mentioned. These three together form the somesthetic area. Stimulation of points in a conscious subject (Cushing & Penfield), evokes sensations referred to the various parts of the opposite half of the body surface. These are tingling, numbness, tactile sensations and even pressure. Pain however, was never elicited by cortical stimulation, raising a doubt about cortical representation for pain. Further, excision of any part of the cortex fails to abolish the pain sensation. Natural stimuli like those of touch, warmth, cold etc. applied to the various regions in the body on the opposite side, caused the occurrence of action potentials which could be recorded from this cortical area (evoked potential technique of Woolsey, Bard and others). It has been seen from these studies that the various sensory regions of the body have representation in an upside down order for the trunk and limbs, but in the 'erect' manner for the neck and head. The trunk occupies an area posteriorly in the gyrus, with the limbs more anteriorly placed (reverse of the situation in motor area). Such parts of the body surface like face, tongue, finger tips, palm of hand, dorsum of foot etc. where a great degree of spatial discrimination for touch as well as high accuracy of tactile localisation obtains, have disproportionately large areas devoted

to them in the postcentral gyrus. The extension of this gyrus on the medial surface of the hemisphere beyond the supero-medial border provides sensory representation for the knee and leg similar to the motor area in the precentral gyrus. Evoked potentials arising from stimulation of the body surface and even of muscles, could be recorded over the motor area just as some degree of motor activity could be elicited from the postcentral gyrus. It is because of these observations that the gyri bounding the central fissure are thought to constitute together, the sensory-motor area, thereby avoiding a watertight division into a separate sensory part (receptive zone) and a motor part (or executive part). A consequence of such a sharing or overlap of function is the hypotonia that is seen as a result of a lesion of the sensory cortex. The loss of a sense of passive movement, may be responsible for this.

The lowest part of the post-central gyrus is the cortical centre for taste which extends to the insular cortex. Stimulation here evokes a "terrific tight sensation of taste". It is significant that the taste area lies close to the motor area for the muscles of mastication.

In addition to the sensory area I in the post-central gyrus, there is a II somatic area in the upper wall of the sylvian fissure below the somatic area I. The body representation here is in the erect posture. Phylogenetically the II area may be older and may be concerned with protopathic or crude sensations, while the I area subserves finer or epicritic aspects of sensory perception. The ipsilateral half of the body is also represented in the area II in addition to the contralateral half. One significant finding is that, when the II area is stimulated, the response to painful stimuli becomes abnormal and exaggerated (Hyperpathia).

There is no modality-wise representation in the sensory cortex, since even the sensory or specific thalamocortical fibres themselves are not organised on this basis, unlike the spinal and lemniscal systems wherein fibres subserving one type of sensation are separated from those catering to other sensations.

The superior parietal lobule containing the areas 5 & 7 are sensory association areas. The area 5 has also been known as the parietal adverse eye field in view of its association with eye

movements which could be elicited on stimulating this area. The parietal lobe as a whole seems to be involved in perceptual or psychic processes leading on to spatial and intensity discrimination as well as stereognosis. A lesion confined to the post-central gyrus does not cause abolition of sensations but depresses the discriminative and related perceptual faculties. There is also an inconstancy of response to stimulation and the affected individual may even be unaware of stimulation now and then. These defects are accentuated when the areas 5 & 7 are also involved in damage. Spatial recognition (tactile and other localisation and tactile discrimination), intensity differences between greater or lesser warmth, greater or lesser cold, greater or lesser pressure etc. are the aspects of sensory function which are depressed. Spatial recognition is more affected in lesions of area 3 (lying farthest anteriorly), intensity discrimination diminished after damage to the supra-marginal and angular gyri, and stereognosis, after injury to middle region of postcentral gyrus. Loss of sensation implies subcortical damage. After removal of the postcentral gyrus, considerable recovery of sensation occurs either due to the activity of the II sensory area of the same side or due to more widespread sensory distribution beyond the areas 3, 1 and 2.

The Supramarginal gyrus (area 40):— Anatomically, this is to be included in the parietal lobe. Its physiological importance is dealt with under 'Aphasia'.

The Temporal lobe: This portion of the cerebral hemisphere is anatomically 'somewhat away from the main stream'. The most well-known centre of cortical function here is the auditory area 41 in the transverse convolution of Heschl, buried in the Sylvian fissure which receives auditory radiations from the medial geniculate body. It is concerned with frequency, intensity and quality analysis of sound waves falling on the ear. In the cat, two auditory areas I & II have been delineated by Woolsey & Walzl. In the former, the cochlea is represented base anteriorly and apex posteriorly and in the latter, in the reverse order. As many as four auditory areas have been revealed by electrophysiological studies in animals. Whether these findings are applicable to the human cortex, remains to be seen. The greater part of the superior temporal gyrus outside the primary auditory area is known as the

audiopsychic area which is concerned with elaboration of auditory sensations. In the posterior region of the superior temporal gyrus (area 22) is a centre related to the equilibratory sense. Lesions of this region cause dizziness, sense of falling, swaying or even rotation. Though memory traces are diffused over the entire cerebral cortex of both hemispheres, the temporal lobe seems to be a special site for storage of memory pictures. Dreams involve recalling of these pictures in somewhat of a jumbled manner and they can be very fantastic as regards the net effect. Contrary to what was known regarding the descending links from the temporal lobe with the pons, recent studies indicate that the parietal lobe sends down fibres to the pons and it is this group of fibres which was erroneously called, formerly, as temporo-pontine fibres. Other connections are not fully established. It is possible that the pulvinar of the thalamus may have two-way connections with the anterolateral parts of this lobe. Their possible role is yet to be elucidated.

Certain well-defined symptom-complexes result from bilateral lesions of the temporal lobe including neocortex and rhinencephalon.

1. Aphasia is a consequence of lesions in posterosuperior part of the temporal lobe involving the supramarginal and angular gyri. More about this is described under 'Aphasia' later on.
2. Hearing disorders also occur. Tinnitus or ringing noises in the ears and even auditory hallucinations may be experienced. Sound stimuli may precipitate an epileptic seizure. Deafness does not result, to any appreciable degree.
3. Smell and taste disturbances may be seen associated with lesions in the anterior part of the temporal lobe.
4. Psychomotor seizures consisting of psychological disorders and motor activities, may be caused. Hallucination concerning auditory, visual or smell sensations may also be experienced.
5. Because of the close proximity of the Meyer's loop, formed by the visual fibres emerging from the lateral geniculate body and as they curve backwards to form the optic radiation close to the external surface of the temporal lobe, it may be interrupted by damage to the temporal lobe. The result will be defects in the visual field like contralateral homonymous hemianopia, especially in the upper quadrants.

Various symptoms like visual agnosia, oral tendencies (attempt to identify objects by putting them into the mouth), hypermetamorphosis (marked tendency to attend to every visual stimulus), extreme tameness and loss of fear and others, have been noticed with experimental lesions of the temporal lobe in monkeys. Each of these symptoms, has been related to loss of function of particular areas in the temporal lobe.

The occipital lobe : Its structure and functions will be considered under 'Physiology of vision'.

THE ELECTROENCEPHALOGRAM (EEG)

Hans Berger was a pioneer in the study of the electroencephalogram. He was able to detect electrical activity of the cortical neurones by placing a pair of plate electrodes on the frontal, parietal and occipital regions, of the cranial vault. A record of such activity was termed the electroencephalogram. A record of potentials obtained by placing electrodes directly on the exposed cerebral cortex during surgical operations, was given the name electrocorticogram. For clinical purposes, the electroencephalogram is adequate. Burger studied the characteristics of electrical activity of the brain and he described each type of such activity. The table below gives some salient details.

	Frequency of waves/sec.	Amplitude of the potential changes (voltage developed)
Alpha rhythm	6—13	20—50 μ V
Beta rhythm	15—60	5—10 μ V
Delta rhythm	0.5—5	20—200 μ V

The records were obtained by using an oscillograph or a sensitive galvanometer with a direct writing device.

Physiological basis : Even when small slabs of grey matter were isolated from the rest of the cortex by vertical cuts, activity persisted, provided these were not also isolated from underlying nerve fibres entering the grey matter. Thermocoagulation of the superficial four layers of the cortex did not abolish this

activity. It is held that the barrage of afferent impulses passing up the nonspecific thalamocortical system of fibres from the thalamus is responsible for this phenomenon. A synchronous and rhythmical discharge from the deeper neurones of the cortex is generated and maintained by the thalamocortical impulses.

Alpha rhythm : This is also known as Berger rhythm. It is best recorded from the occipital or occipito-parietal region of the head. It indicates mental inattention in a wakeful state with the eyes closed. Even opening the eyes may terminate it and bring on Beta rhythm which is indicative of active mental processes. Tactile and other stimuli interfere with this type of activity (α rhythm).

Delta rhythm : This is seen in children as a normal feature, whereas in adults in the wakeful state, it is definitely pathological unless provoked by voluntary hyperpnoea. In adults, it is normally seen during sleep.

Clinical use of the electroencephalogram : Epilepsy or pre-epileptic states can be detected by the study of the EEG which shows abnormal features. Cerebral tumours can be roughly localised by means of the EEG.

Sleep : Changes occur in the normal 'waking' pattern during sleep. In light sleep, alpha rhythm may occur, changing on to delta type in deeper sleep. What are known as sleep spindles may supervene in deep sleep.

The study of the EEG is a specialised one like that of the ECG (electrocardiogram)

APHASIA

Literally, it means loss of vocal speech. This is a disorder said to be in the psychic sphere—i. e. at the higher neural levels—without any involvement of the peripheral neuromuscular apparatus (paralysis of muscles of the larynx, nasal, oral and pharyngeal region). There is a failure in the comprehension and use of symbols in the reception, formulation and transmission of ideas. The general intelligence may not be impaired to any appreciable degree.

From the time of Broca, the Parisian neurologist, the different aspect of reception and transmission of ideas were ascribed to certain circumscribed areas of the cerebral cortex, especially of the dominant hemisphere. Broca identified the area 44 (of Brodmann) in the inferior frontal convolution just in front of the lowest part of the prefrontal gyrus, as the glossokinesthetic area, on account of loss of speech in a few individuals who were seen to have, at autopsy, lesions in this region. This led to the other neurologists to localise the various components of the speech mechanism as follows:

Glossokinesthetic area— (vocal speech)	Posterior part of the third frontal convolution (area 44 of Broca).
Cheirokinesthetic area— (hand area for writing)	Posterior part of the second frontal convolution.
Centre for reception of spoken word—	Superior temporal convolution. (posterior part)
Centre for reception of written word—	Angular gyrus.

The last two are known together as the Wernicke's sensory area.

While Broca postulated that the command for spoken word formulation given to the peripheral apparatus for actual execution—causing pronunciation of the syllables in the words—originated in area 44, experimentally it has actually been shown that in conscious subjects, stimulation of this area in the dominant hemisphere caused arrest of speech and not production of words. Likewise, cessation of speech has been caused by stimulation of three more areas — a region on the medial surface of the hemisphere anterior to the motor area for the leg, an area in the parietal lobe behind the lowest part of the postcentral gyrus and the posterior part of the temporal lobe — all in the dominant hemisphere. The significance of this finding is not yet clear. Vocalisation was not elicited by stimulation of the head and neck area in the precentral gyrus.

The older neurologists described at least four different categories of aphasia.

1. **Motor aphasia** — The formulation of spoken words at higher neural levels was either lost or defective. This was held to be due to a lesion of the Broca's area.
2. **Agraphia** — Inability to compose the necessary words for writing. This was thought to result from a lesion of the cheirokinesthetic area.
3. **Word blindness (visual aphasia or alexia)** — Damage to the angular gyrus was considered to be responsible for this defect. While an afflicted subject could copy written words, he could not make out the meaning of those words. This is akin to the inability in a normal man who, while he is familiar with a particular alphabet, is a stranger to a language which utilises them as in the case of an English man who is ignorant of the French language and so cannot understand words of that language even though the alphabet are the same.
4. **Word deafness** — (auditory aphasia) — An inability to comprehend words spoken by others. This is like a normal person who can repeat what he hears in a language unknown to him, though the sounds are devoid of any meaning or significance to him. Injury to the supramarginal gyrus was taken to be the cause of this type of aphasia. Cases of (1) & (2) types were considered to be motor aphasias, and word deafness and blindness as sensory aphasias.

Sir Henry Head denied such a cause and effect relationship between localised lesions of the cortex and aphasias, implied by the older ideas described above. He contemptuously called the originators of such ideas as 'diagram makers'. Head redivided the different types of aphasia into four categories. The older classification into purely motor and purely sensory aphasias could not be sustained as each patient presented a picture of both motor and sensory deficits. Head's division is as follows:

1. Nominal aphasia
2. Verbal defects
3. Syntactic aphasia
4. Semantic aphasia

1. As regards Nominal aphasia, there is inability to recall names of familiar objects shown to the patient. The word-image is absent in the memory store. However, the use to which the object can be put is remembered. Thus, while a pen cannot be named, its use in writing is remembered.
2. Verbal defects — An inability to utter words signifies this state. The power of expression of ideas is lost. A few ejaculatory type of words escape from the mouth without context or cause. Mispronunciation of individual words, though sentences may not be wrongly constructed, may occur in mild forms of this condition.
3. Syntactical aphasia — While single words by themselves may be uttered clearly, the normal or grammatical sequence may be absent in a sentence. Full sentences cannot be formed to express an idea. In some cases the total effect resembles baby talk because of slurring over in mouthing the words.
4. Semantic aphasia—The victim of this condition will not have any of the defects of the other three types but he is unable to grasp the overall significance or meaning of a sequence of words or a sentence, an entire picture or painting. While the details are identified and pointed out, the total significance of what he hears or sees escapes him.

Head's studies enabled a correlation between lesions and the types of aphasia, to some extent. Verbal defects seemed to arise from lesions of area 44 and the region behind the lowest part of the postcentral gyrus, while lesions of the supramarginal gyrus and the temporal lobe seemed to be responsible for the production of semantic and syntactic defects, respectively. Head devised certain simple tests, to assign a patient, to a particular category.

There does not seem to be a strict regionwise distribution of functions in the cerebral cortex, each area being responsible for one aspect of speech. All that can be surmised from various studies is that, when particular areas are damaged, the apparent defects are not due to loss of function of these areas but due to interruption of long association pathways which converge at these sites and again diverge away forming knots, as it were. At such sites, a lesion will interrupt most of the fibres, causing

thereby the particular defect in speech. There is some rethinking on Head's views. Much more will have to be unravelled about speech mechanisms before one can have a clearer view of this problem.

Apraxia is a term referring to an inability to carry out a voluntary movement either on request or in imitation. Apraxia is also said to be of motor and sensory types. Sensory apraxia means inability to know the significance or use of objects seen—what to do with or how to use an object purposefully. Aphasia, at least of the motor variety, is apraxia of the speech faculty.

SPEECH MECHANISMS

Speech is a special faculty of the human species. The mode of communication between one human being and another is known as conventional speech. Even animals can indulge in a form of establishing contact with each other by means of primitive 'speech' which takes the form of attitudes of the various parts of the body (as in animals)—limbs and tail; gestures and sounds like grunts, hissing and growling. Primitive or natural speech is also used by man in addition to ordinary speech.

The generation of spoken words requires the despatch of commands from the speech area of the brain (not yet located) to the peripheral voice apparatus of the larynx and various other muscles involved. In issuing orders, the cerebral cortex makes use of the feedback from the end organ of hearing. This is a necessary component of speech. Deaf mutes are deprived of this feedback from the ear, from childhood and hence, their speech faculty cannot develop spontaneously. With special hearing aids used from an early age, these individuals can be made to learn to speak.

Mechanism of speech: When expired air is driven past the vocal cords by bellows action of lungs and chest wall, the vocal cords vibrate and the vibrations are modified by their passage through pharynx, nose and mouth. Speech is produced during expiration. The vocal cords stretch from the thyroid cartilage in front, to the mobile arytenoid cartilages at the back. The

muscles controlling the arytenoids, close or open the glottis. The thyro-arytenoid muscle in each cord regulates the tension in that cord and the cricothyroid muscle tilts the thyroid cartilage and elongates the vocal cord. The vocal cords open out on inspiration and come together in expiration. They are slightly parted in death. The vocal cords are approximated during phonation. The tongue, by its position and shape assumed, alters the resonant properties of the oral cavity, but the lips and jaws are also involved in the production of speech.

The vagus furnishes not only sensory but also motor fibres to the larynx. The superior laryngeal branch of the vagus with which, a twig from the sympathetic nerves mingles, divides into two branches, the internal and external laryngeal nerves. The former is sensory to the upper part of the larynx, while the latter provides motor fibres to the cricothyroid muscle. The recurrent laryngeal nerve, a direct branch of the vagus, supplies motor fibres to all the intrinsic muscles of the larynx except the cricothyroid. It also conveys sensory fibres meant for the lower part of the larynx. An injury to the recurrent laryngeal nerve of one side, results in hoarseness of voice. If the nerves on both sides are affected, paralysis of vocal cords will be the consequence.

Vowels are produced by vibrations of the larynx. Whispering does not involve the use of the vocal cords much. Consonants arise in the mouth (mostly) when an expiratory blast or puff of air is obstructed voluntarily by placing certain structures in its path. Depending on the anatomical part used for this purpose, consonants are classified as labials — p and m (lips); dentals — th (upper and lower front teeth with the tip of the tongue intervening); gutturals — g in game (tongue opposed to the palate). Certain consonants are known as labio-dentals, labio-gutturals and palatals, which are produced by placing more than one anatomical part in the path of the air. Stopped consonants are produced by completely obstructing the expiratory flow — b and p. Nasal consonants — m and n — arise by diverting the passage of air into the nose and not at all through the mouth. Open consonants are generated when the expired air is forced through a narrowed passage in the mouth — s and z.

The mouth, pharynx and the nose seen to be even more important than the larynx itself, in the production of audible syllables. This is suggested by the fact that subjects in whom the larynx has been surgically removed for the treatment of malignant growths, can be trained to regain speech. In these people, air is trapped in the oesophagus and its emission into the pharynx and the mouth is controlled voluntarily in bringing about the utterance of words.

Certain terms can be defined in this context :

Anarthria or dysarthria : Words can be mentally formulated but cannot be articulated properly owing to a defect in the peripheral speech-producing apparatus (peripheral motor nerves and muscles).

Palilalia : Repetition of phrases as seen sometimes in Parkinsonism.

Mutism : Complete loss of speech without an organic basis.

Aphonia : Inability to phonate audibly. The voice assumes a whispering quality due to a lesion in the vocal cords or the muscles motivating it.

THE CONDITIONED REFLEXES

Conditioned reflexes utilise very long chains of neurones, both in the afferent and efferent limbs, the reflex centre itself being of a very complex organisation. A component of this centre lies in one of the sensory areas of the cortex and these are termed analysers, since they are responsible for very accurate and minute analysis of the stimuli leading on to discriminations as regards modality and submodality and also between various intensities of the same type of stimulus. It can be truly said that the day to day life of a civilised man is just a series of conditioned reflexes occurring one after the other from the time of waking up to the instant one drops asleep. Pavlov, the famous Russian Nobel laureate, established the physiological basis of the conditioned reflexes and evolved suitable terminology for this purpose. The advancement of knowledge, especially in the sensory aspects of neurophysiology, owes not a little to the

use of conditioned reflexes in the methodology of experimental studies, especially in the case of colour vision, auditory discrimination etc.

A conditioned reflex is not innate or inborn in an individual of the species. It is developed in close association with or based upon a natural or inborn reflex, the stimuli for the two reflexes being presented together in order to establish a firm relationship between them and thereby transferring the response of the inborn reflex to the acquired reflex. The response to a conditioned stimulus however, differs in certain respect, from that to the unconditioned stimulus. The conditioned stimulus and the unconditioned stimulus are presented with varying intervals between them, in each of which case a special term is used to denote the particular kind of conditioned reflex. As a result of the large amount of data accumulated, it is possible to compare the features of a conditioned reflex with that of an unconditioned reflex.

<i>Inborn reflex</i> (natural or unconditioned)	<i>Conditional reflex</i> (acquired reflex)
1. No training is required to establish this.	1. Training (sometimes even very laborious) is a prerequisite.
2. Inherited by all individuals of the species.	2. Only the particular animal which is specially trained, exhibits the reflex.
3. This is stable and not lost during the course of illness or disuse.	3. This has to be frequently reinforced to last or persist. Otherwise it will disappear.
4. This type is of a small number, associated with the living habits and bodily function of the animal.	4. A wide variety, comparatively speaking, can be established in any animal.
5. The nerve pathways involved are short and peculiar to the reflex and anatomically well worked out in detail.	5. The nerve channels are very complicated and cannot be unravelled easily.
6. The integrity of the cerebral cortex is not essential for the occurrence of the reflex.	6. Cerebral centres (analysers) are absolutely essential for setting up this type of reflex.

It is however, necessary to determine (even after realising the differences between inborn and acquired reflexes) which are really inborn reflexes. A young animal, if separated from its mother from birth itself and fed on a diet not usual for the species, may not evince interest in the food normal to its kind. Thus, some reflexes, apparently inborn, are really not natural to the species.

Certain basic requirements have to be satisfied if an animal is to be conditioned to a particular stimulus. It should be in a healthy state, i. e. – free from illness. This probably is so, because an alert creature can be more easily trained than a sick animal, in which it may not be possible to be sure of its attentiveness. Distraction by extraneous stimuli should be totally avoided during the training period. Painful stimuli, as a rule, should not be employed as conditioned stimuli, as defensive responses are put out. Stimuli should be clearly above threshold values in order to be certain of a response. Repetition of the stimulus is necessary to establish the reflex. Once this has been achieved, there should be reinforcement now and then.

Pavlov's studies: The dog was the experimental animal. It was kept in a room free from distracting stimuli. It was put in a harness so as to restrict bodily movements. The presentation of food (meat powder) was the unconditioned stimulus. The ticking of a metronome (sound as a stimulus) was the conditioned stimulus. Salivary secretion was the response obtained. The saliva produced was collected by means of a fistula in the duct of the salivary gland (the opening of the duct is transplanted to the cheek) and its volume measured with a convenient device. The observer remained outside, during the course of the experiment. Quantitative information could be obtained in this way. After the conditioned reflex was established, mere sound stimulus evoked the salivary secretion.

As regards subsequent studies by other workers in this field, the actual experimental details varied depending on the mode of stimulation and the type of response obtained. A vast body of knowledge has been built up by many investigators using a wide variety of stimuli.

Conditioned reflexes are of various types named after the mode or sequence of presentation of the two stimuli—conditioned and unconditioned.

1. *Simultaneous conditioned reflex* — The two stimuli are presented to the animal together, without any interval of time between them. This is the easiest type to establish, since the association between the stimuli is most easily impressed in the mind of the animal.
2. *Delayed conditioned reflex* — A certain interval is allowed to elapse between the onset of the two types of stimuli. The conditioned stimulus is applied in advance of the unconditioned one, the former being continued till the latter is presented to the animal.
3. *Trace reflex* — The conditioned stimulus ceases after a very brief duration and there is a very short interval before the unconditioned stimulus is commenced. It is not easy to set up this variety of conditioned reflex.
4. *Temporal conditioning* — When an unconditioned stimulus occurs at regular intervals of time, the response occurs as soon as the particular chosen interval of time elapses and this itself takes on the role of a conditioned stimulus. Thus, if a dog is fed, say, once in every three hours, the passage of three hours time after a meal will itself provoke a salivary response.
5. *Backward conditioning* — The sequence of the stimuli is reversed, the conditioned stimulus following the unconditioned one. This type of reflex is rather difficult to establish, though not as much as in the case of the trace reflex.

Conditioned reflexes of higher orders : When, say, a conditioned reflex is established for a sound stimulus, a flash of light as a stimulus is repeatedly presented along with the sound stimulus, the mere flash will evoke a response. This will be a reflex of the second order. Likewise, reflexes of higher orders may be set up. The stimuli used for higher order reflexes are said to be linked up with that of the first order. Responses of the alimentary canal cannot be evoked by reflexes of higher than second order. In any case, it is not possible to reach beyond the third order of conditioned reflexes.

Properties of conditioned reflexes

Specificity — A conditioned stimulus will evoke the same responses again and again and no other.

Summation — If two conditioned stimuli elicit the same effect when presented separately, their effects will be summated when the stimuli are presented together.

As has been pointed out already, a conditioned reflex will wane away if the conditioned stimulus is not reinforced with the unconditioned stimulus frequently. The disappearance or even inhibition of a conditioned reflex can be brought about under a variety of circumstances. The loss of a conditioned reflex is broadly due to two mechanisms. 1. External inhibition—when a conditioned reflex has been established, if a stimulus, like a loud sound is presented in between the conditioned stimulus and the unconditioned one (as in Pavlov's experiments), the animal's attention is diverted to the new or strange stimulus. The animal exhibits curiosity as regards the distracting stimulus and fails to put forth the expected response of the conditioned reflex. The distraction is said to give rise to an investigatory reflex which keeps in abeyance, the conditioned reflex.

2. Internal inhibition – This itself is of several kinds.

a) Extinction – When the conditioned stimulus is applied a number of times without being followed by the natural or unconditioned stimulus, the reflex is said to undergo extinction. The experimental animal (in the case of Pavlov's dog) begins to dissociate the two stimuli since they do not occur together. The dog cannot any more, confidently expect the food to be offered when the sound stimulus is infrequently or not at all accompanied by the meat powder.

Disinhibition or spontaneous recovery of a conditioned reflex:- After a conditioned reflex has suffered extinction, an extraneous stimulus may cause the revival of the reflex. This action resembles the case of external inhibition, in which the extraneous stimulus inhibits the reflex. In spontaneous recovery, the new stimulus abolishes the inhibition.

b) **Conditioned inhibition** – To quote Pavlov's experiment again, when the conditioned response has been set up for the ticking of a metronome and the reflex reinforced frequently, if however, a second stimulus like a flash of light is paired with the sound stimulus without reinforcement by the natural stimulus, the flash of light will take the role of an inhibitory 'stimulus'.

c) **Inhibition by delay** – After establishing a 'simultaneous' conditioned reflex, if the conditioned stimulus is continued for longer and longer duration on each successive day before the unconditioned stimulus is presented, the latent period (before the response came on) which was very short in the beginning, now lengthens out. The simultaneous reflex has become a 'delayed' reflex. The progressively later and later onset of the unconditioned stimulus has prevented the immediate commencement of the response, putting it off to a more distant moment.

d) **Differential inhibition** – When a particular stimulus, for eg. – a pure tone of a particular frequency, is used as a conditioned stimulus, if it is replaced by a tone sufficiently different in frequency, the latter fails to be effective. The cortex – 'auditory analyser' distinguishes between the original stimulus and its close substitute. This property has been utilised in the determination of hue discrimination, tonal discrimination, intensity discrimination etc., in animals. It is from such studies only that it has been concluded that most mammals are colour blind.

As opposed to differential inhibition, there is stimulus generalisation (irradiation) – If one stimulus is used for training an animal, it may respond to another, very closely resembling the first in its various parameters. But, as the differences between the two stimuli become wider, differential inhibition will occur. Generalisation of extinction refers to the inhibition of the effects of anyone of a number of stimuli closely resembling each other in spatial, intensity or other characteristics (stimulus generalisation), if one of these is previously subjected to conditioned inhibition referred to above. When recovery of the effectiveness of the stimuli occurs, the inhibition is confined to the one stimulus for which conditioned inhibition was first established (concentration). The term irradiation is particularly applied to

the involvement of neighbouring areas of the cortex around the one mainly affected (the analyser) with spread of the effectiveness of inhibition and concentration to the release of the neighbouring areas from the inhibitory effect.

Experimental neurosis – When an animal has been trained to respond to, say, a tone of a chosen frequency, confusion may arise in its mind if closely related stimuli are employed. Discrimination among these stimuli may fail and the state of experimental neurosis may result. This manifests itself as an unstable mental condition with tantrums of temper and violent behaviour. Difficulties in discrimination may bring about such symptoms in human beings also.

Interoceptive conditioning – The conditioned reflexes studied by Pavlov and others involved the application of sound stimuli, flashes of light and such which excited the exteroceptors. These reflexes have now been extended to activate interoceptors like baroreceptors and chemoreceptors of the carotid regions. Conditioned reflexes based on the stimulation of exteroceptors which are linked with the responses of the interoceptors, are the latest developments. The increase in pulmonary ventilation consequent on hypercapnia, can now be evoked as a response to a conditioned stimulus of sound or light flash or of any other type. This is a rather revolutionary sequel in the study of conditioned reflexes.

LEARNING AND MEMORY

The ability to acquire new experiences and integrate them with past ones, in other words to learn or to increase the knowledge content of the brain, is a well recognized characteristic of higher animals and man. It is a faculty of even lower animals including invertebrates like the octopus. But, phylogenetically higher animals can be trained to a much greater extent than those of lower orders. The nervous system is very necessary for the process of learning and also for the consequent phenomenon of memory. The nervous system also exhibits amazing recuperative powers (recovery) after injuries. The memory of facts learned and of acts trained for, most often survives gross damage to the brain as occurs in severe neurological disorders or after trauma.

The mechanism of learning has been investigated, making use of conditioned reflexes, in experimental animals, which either passively put forth responses as in Pavlov's classical studies, or actively handle mechanical gadgets (instrumental conditioning) like levers and such, in order to obtain for themselves rewards in the form of food. In fact, conditioned reflexes themselves constitute one type of learning process. The questions involved in learning and memory are - 1. How is information (memory) stored in the brain? - Is it in a single cell or in a collection of cells or diffusely over the entire brain? 2) What is the molecular basis of memory? 3) How is the brain organized to enable learning processes to take place?

Many instrumental aids or devices have been invented to carry out studies in instrumental conditioning. It is too early to make any assessment of such studies and explain learning in the light of the results obtained from them.

Studies have been undertaken to find out the neurological basis of learning. Pavlov thought of analysers as being responsible for the establishment and effecting of conditioned reflexes. Loucks stimulated appropriate neural pathways directly and obtained responses which were the same as those for previously established conditioned reflexes. Where exactly in the nervous pathways in the brain, the conditioned and unconditioned reflex arcs were linked up, could not be revealed by these studies. It has been found very difficult to establish conditioned reflexes occurring purely at lower levels (mediated by the spinal cord). In mammals, conditioned reflexes established before experimental cortical damage, could be reestablished after removal of parts of the cortex, though in a much cruder way. The cortex seems to be the organ of learning even in lower animals, though it is not the only such organ. Subcortical parts of the brain can, to a great extent though not fully, replace the cerebral cortex in this regard. An animal which has been accustomed or habituated to a distracting stimulus giving rise to the investigatory reflex, seems to respond less and less to the same excitant with the passage of time, as shown by the diminution of the recorded electrical activity of the brain. But it must be said that it is not possible to satisfactorily correlate

behaviour with electrical activity in the present state of knowledge.

It has to be admitted in conclusion, that not much is known about the neural mechanisms underlying the learning process. Some general observations have been made from objective and subjective studies. The capacity to learn and the rate of learning increases from the birth to about the 15th year of age and slow decline sets in from then on. Penfield was of the opinion that children could learn new languages more easily than adults. He even seems to have believed in the existence of a language centre in the cortex, which was active in childhood, thereby conferring the ability on children to learn new tongues. In adulthood, this centre seems to be far less active. The knowledge level (quantity of information stored in the brain) attains a maximum towards the end of the third decade of life, after which it falls owing to an increase in the rate of forgetting which approaches a maximum at about 60 years of age and continues so, for the rest of the life.

Memory: Memory implies the ability to recall past experiences originating from events, facts, people, animals and objects. The establishment of a memory is intimately associated with the process of learning. Lashley, from his work on ablation of cortex, concluded that memory is stored in a diffuse manner all over the cerebral cortex. He coined the term 'engram' to represent the neural state characteristic of learning a particular act or storing a fact. It was seen by him that removal of parts of the motor cortex made the animal clumsy in performing the acts for which it was previously trained, though it retained the knowledge of what exactly it had to do. The pattern of motor activity required was remembered, though its execution suffered. It has been held by neurologists that the association areas were responsible for storing memories. For eg.—the visual association areas in the occipital lobe (areas 18 and 19), were considered to be instrumental in recapitulating the memory for objects or patterns seen by the eye, but removal of these centres did not abolish visual memories. On the other hand, lesions in the area 21 in the inferior part of the temporal lobe in the monkey, caused interference with the retention of memories. Stimulation of points on the surface of the temporal lobe brought forth memories of the past, surpassing in detail anything that

could be voluntarily recalled. These flashbacks ceased on stopping the stimulation. Some triggering mechanism (key) for initiating the recall of memory, may exist in the temporal lobe. Lesions in the frontal lobe made memory of objects seen in the immediate past disappear. The experiments of Bikov and later Myers, has shown that a memory trace (a temporary image) set up by a sensory experience in one cerebral hemisphere in a particular lobe — occipital lobe in the case of vision — was later transferred through the corpus callosum to the opposite cerebral hemisphere. A particular engram, in other words, is set up not only in one hemisphere but also in the opposite hemisphere. This is unlike what Lashley conceived of in this regard. He believed that the engram was diffusely spread over the entire cerebral cortex, but the work involving sectioning of corpus callosum indicates that memory engrams are stored in many parts of the brain, one in each and not in a diffuse way.

Memory is of two kinds — short term and long term. When a sensory experience has been acquired, it is provisionally stored in the brain as a memory trace. If it is not consolidated, it may disappear. Events like concussion and severe electric shocks, may abolish memory traces, but not memories which have been consolidated. This process of converting the memory traces into permanent engrams, takes some time. The consolidation of memory to convert a memory trace into a long lasting impression or engram, is helped by reinforcing the memory trace by frequent recall of the remembered mental pictures. In the early stages of consolidation, repetition of the stimuli which gave rise to the memory trace, like looking at a page of written matter to be memorised, again and again, facilitates the processes of indelibly 'etching' (so to say) the memorised facts on the brain (mind). Certain factors like electroconvulsive shocks and great fear may disrupt consolidation of memories.

The structural basis of memory: Short term memory (memory trace) seems to be maintained by impulses travelling cyclically in closed circuits of nerve cells activating each other and prolonging the activity of the circuits. It is liable to be lost easily. Long term memory cannot be sustained by constantly active nerve circuits, since it persists even after damage to the

brain or anaesthesia. Structural changes in the nervous elements comprising a synapse, have been thought of as a basis of long term memory. Post-tetanic potentiation – the facilitation, at the postsynaptic membrane resulting from faradic stimulation of a presynaptic nerve fibre over some time – lasts for even some hours. This phenomenon may probably be involved in long term memory or at least memory lasting for more than a few minutes. Memory stored over months and years requires a different explanation. A suggestion has been made that the area of contact between two neurones at a synapse may increase with repeated passage of impulses across the synapse. Even newer buttons terminaux may be put out to increase synaptic contact between two nerve cells.

The giant molecules of DNA and RNA in the genes can store a large amount of information concerning inherited characteristics and the sequence of aminoacids for the synthesis of proteins. It is speculated that these substances can store long term memory in the form of slight alterations in the molecular configuration. Some indirect evidence has accumulated in favour of this idea. Certain worms which were trained to avoid stimuli in the form of bright light, retained their ability to recognise the unpleasant stimuli even when they were cut into two and each half regenerated to form a complete worm. This has been sought to be explained on a chemical basis. The trained worm may have a stable alteration of its RNA which passes on to the daughter worms perpetuating their ability to shun light. The enzyme, ribonuclease, renders the worms incapable of learning to avoid the stimuli (light) to which the untreated worms can be made sensitive. Increased RNA synthesis and breakdown occurs in mammalian nerve cells which are stimulated intensely. Some additional facts in this regard have accumulated to implicate RNA in the mechanisms underlying memory. It is not known at present as to how nerve impulses which preliminarily set up memory traces can bring about such molecular changes and how these in turn can be retranslated into nerve impulses when memories are recalled. The possibility that neuroglial cells may have a role in this function of the brain has been suggested, but more has to be found about this.

Loss of memory (amnesia) is most often temporary. Even normal individuals are sometimes unable to recall their memories

at will. At other times, the mind wanders about causing the recapitulation of the past. Korsakoff's psychosis is a condition resulting from chronic alcoholism wherein memory for recent events is lost, while that for the remote past is retained. So also in old age.

THE PHYSIOLOGY OF SLEEP

Sleep is a state of unconsciousness which occurs at intervals, and usually lasting for some hours continuously, either in the night or less often in the day time. In infants and young children, short periods of sleep alternate with similar periods of wakefulness. Sleep differs from coma in that, in the latter, the individual cannot be aroused even by strong stimuli. Also after sleep, the animal or human subject wakes up almost spontaneously, whereas in coma, unless the cause is treated, the afflicted individual cannot regain consciousness.

The requirement of sleep (the duration of sleep) depends on the age. Infants sleep during most of the 24 hours with several short intervals of wakefulness. As the child grows up, there is a gradual diminution in the duration of sleep required. In adulthood, about 7-9 hours of sleep is sufficient. This depends on the amount of manual work performed, to a large extent. In old age, a few hours of sleep in the night, supplemented by short naps in the daytime will do. In case sleep is denied on a particular day or even for two or three days in succession, the deficit or arrears can be cleared by sleeping for one night and full recovery from fatigue takes place. The effects of prolonged deprivation of sleep have been studied in dogs and in human volunteers. While the physical effects were not noticeable in recent studies, some degree of lack of mental concentration and even confusion with loss of memory was seen in almost all human subjects. Young animals and children were affected more by loss of sleep, than adults. The exact role of sleep in the physiological economy of the animal is still to be worked out. According to the experience of all, sleep is a state of rest necessary for the recuperation of 'mental' and physical 'energies' so necessary for the continuance of life, day after day. It is not possible at the present juncture to say more in this regard.

Course of sleep: The threshold for stimulation for awakening denotes the depth of sleep. For an hour after the onset of sleep, the depth of sleep increases and later it declines, initially sharply and later more gradually. In children, two depth maxima are observed, one during the first hour and the other several hours later. Daytime naps are of less depth than slumber at night. No dreams occur in deep sleep.

Physiological effects of sleep:

a) Nervous system – A state of drowsiness lasting for a few minutes, usually precedes sleep. In cases of extreme fatigue, sleep may come on rather suddenly. Sensory functions are depressed. The sense of smell is the first one to diminish and later, the others. Righting reflexes are absent; a sleeping person can be easily disturbed without an attempt by him to correct his position or prevent a fall from the cot. Muscle tone is very much diminished. Knee jerk is absent and a positive Babinski sign is seen. Stronger stimuli are needed to evoke most body reflexes. The electroencephalogram (EEG) shows progressive changes with the onset of drowsiness followed by sleep of increasing depth. Five stages in the alteration of the EEG pattern have been described by Davis and others. The alpha rhythm of wakefulness (stage A) yields place to the diminution of the rate of alpha rhythm in the stage of drowsiness (stage B) with low voltage fluctuations and a few delta waves now and then. In stage C of light sleep, spindles superposed over a background of low delta wave pattern, occur. This is succeeded by medium sleep (stage D) characterised by a fall in delta wave frequency though with augmented voltage and disappearance of spindle bursts. In the stage of deep sleep (stage E), delta waves assume prominence with increased amplitude and duration.

It has already been mentioned that the depth of sleep is gauged by the threshold for arousal. In certain phases of sleep which, because of difficulty of arousal, resemble deep sleep, the EEG pattern is that of light sleep. Such a condition is called paradoxical sleep. Light reflex is present though pupils are constricted. Eyeballs are turned upwards and outwards during sleep.

b) *Cardiovascular system*: A general depression of the cardiovascular functions as well as those of the respiratory system is a consequence of the state of sleep. The heart rate shows a fall by as much as 10-30 beats per minute. The blood pressure falls in the first three or four hours of sleep by 10-30 mms Hg and later, slowly rises upto the waking moment. When exciting dreams occur, the blood pressure may show some rise. Vaso-motor reflexes may however, be more active in sleep.

c) *Respiratory system*: Slowing of the rate and fall in depth may occur with costal type of respiration predominating. Periodic respiration of Cheyne Stoke's type may be seen.

d) *Excretory system*: Urinary output is reduced with a fall in concentration of urine. Sweat secretion is increased.

e) *Digestive system*: If at all, an increase of gastric secretion may occur. The movements of the alimentary tract may show an increase in frequency and vigour over those in the wakeful state. Saliva may decrease in amount.

f) *Metabolism*: A fall in the metabolic rate is seen. It may be to the extent of 10-15%. Heat regulation is less efficient.

In general, it appears as if the parasympathetic system has a dominant role over the sympathetic system during sleep.

What brings on sleep, was a highly speculative field till recently. Some of the older ideas were attractive. According to the neurone theory, during sleep, synaptic gaps widened causing a suspension of nervous activity. Another view existed that ischemia of the brain brought on sleep. Chemical theories were also postulated. One was that products of fatigue, like lactic acid, accumulated during the day and when their blood levels rose up, cortical function was affected. A mysterious substance known as hypnotoxin produced by brain cells, was supposed to produce sleep. Extracts from the brain of a sleeping animal were injected into other animals which were found to fall asleep after the injection. These results could not be confirmed by other workers. The pituitary was said to release a sleep inducing 'bromhormone' at a higher rate in sleep than in the wakeful period. No definite evidence is available in favour of any one of the above views.

Pavlov considered sleep as a case of internal inhibition since in experimental animals, sleep followed internal inhibition, induced experimentally. This happened even when differential inhibition (see conditioned reflex) was induced. Drugs like caffeine which depressed internal inhibition, also prevented the onset of sleep. Bromides had opposite effects. Repeated stimuli of a monotonous nature, as in listening to a dull lecture or the reading of a book in a routine manner, brings on sleep. Further, conducive surroundings, as in a quiet room darkened in preparation for retiring, the relaxed position of the body in bed, and the closure of the eyelids, all act as inhibitory conditioned stimuli. Of the older hypotheses, that of Kleitman has some merit in that, it conforms to the modern ideas on sleep. This author thought of sleep, as the result of cortical inactivity brought on by the cessation of impulses from the sensory end organs. When in a quiet dark room, lying on a comfortable bed with eyes closed, there is very little excitation of the peripheral exteroceptors. Fatigue of muscles, enforcing rest, will quieten the proprioceptors in the muscles. Thus, when the cortex is bereft of the afferent drive from most of the receptors, it will quieten down. Some experimental evidence was produced by Kleitman to support his ideas.

Reticular formation and the basis for sleep: In a wakeful animal, the EEG shows high frequency and low voltage discharge. Bremer, in Belgium, transected the medulla under anaesthesia, just above the first cervical segment of the cord (encephale Isolé). This division did not cause any appreciable change in the nature of the EEG. The animal was kept alive by artificial respiration. In this preparation, the cerebral cortex received the afferent flux of the auditory, visual, trigeminal, taste and smell as well as proprioceptive impulses, via the various cranial nerves. When the optic nerves were cut, the occipital lobe gave rise to a different form of electrical activity from the original fast-low voltage waves. Bursts of high amplitude waves resulted from such a section of optic nerves.

A midbrain transection at the level of the Colliculi, posterior to the third nerve nuclei (Cerveau Isolé), caused 'synchronisation' of the fast-low voltage activity of the brain, a characteristic

pattern of records of sleep – bursts of alpha waves separated by pauses of an invariable length – was thereby established. Bremer attributed this radical change in the EEG to the loss of sensory impulses along the cranial nerves. In the encephale Isole animal, the activity of the cranial nerves was sufficient to maintain the normal waking activity in the EEG, even with the interruption of ascending sensory tracts of the spinal cord. In the Cerveau Isole preparation, there was almost total deprivation of sensory information to the brain which now resembled that in the sleeping state.

While Bremer's conclusions pointed in the right direction as regards the basis of sleep, it was given to Magoun and Moruzzi to hit the nail on the head by providing the right explanation for Bremer's findings. The discovery of the reticular system, especially that of the ascending reticular activating system, gave the anatomical basis for explaining the underlying mechanism of sleep.

Contrary to the conclusion of Bremer, lesions placed in the sensory pathways did not bring on sleep or similar states. On the other hand interruption of the reticular fibres (ARAS) in the diencephalic region or the brain stem brought about changes in EEG as well as a sleep-like state. Stimulation of retina or cochlea caused electrical activity in the reticular system. The ARAS receives collaterals from most sensory pathways. Stimulation of the reticular fibres results in 'desynchronisation' of the EEG (low voltage fast waves). Impulses traversing the reticular fibres, activate the entire cortex, unlike those ascending up purely sensory pathways which affect only the receiving cortical areas. The ascending reticular system is responsible for alertness or consciousness. It causes a 'recruiting response' (in the cortex) or a desynchronisation. In the absence of impulses passing through the ascending reticular fibres, the thalamocortical circuits maintain a resting pattern of waxing and waning alpha rhythm. Activity in the ascending reticular fibres puts a stop to the resting pattern of EEG and brings about the arousal response.

In short, it is the absence of impulses ascending the reticular system that causes 'synchronisation' of the EEG, signifying the state of sleep. The opinion of Kleitman is valid seen in the light

of the findings of Magoun and others. When the sensory systems are 'switched off' so to say, the ascending reticular system also becomes quietened and sleep ensues.

Centres for sleep: It was found by some workers that, stimulation of wide cortical areas caused desynchronisation just as in the case of ARAS. Excitation of certain other areas evoked the arousal response in a somnolent animal (the result of certain lesions in lateral hypothalamus and mammillary bodies or the tract of Vicq of Azyr). Stimulation of these areas, on the contrary, made the animals alert. The mammillary bodies seem to be more important of the two hypothalamic regions.

As a centre in control of sleep, the preoptic nucleus seem to be implicated in hastening the onset of sleep. Lesions of this region made the animal continuously wakeful. Stimulation of this nucleus on both sides made the animal fall asleep. It is concluded that the pro-optic nucleus acting as a centre for sleep, inhibits the mammillary bodies.

According to Hess, the predominant sleep centre is in a region lateral to the ventral portion of the massa intermedia of the thalamus. Stimulation with implanted electrodes produces all the changes characteristic of sleep in the proper sequence, like yawning, closure of the eyes followed by sleep.

Even in the case of the thalamic and hypothalamic sleep centres, there is a cortical control from the orbital areas of the cortex which have reciprocal connections with the intrinsic nuclei of the thalamus. Lesions of the orbital areas abolished the recruiting response, induced from the thalamus as well as spontaneous spindle bursts. Since the same areas of the thalamus are involved in both, producing sleep as well as wakefulness, it appears that the frequency of stimulation may be related to the effect caused. Low frequency stimulation gives rise to sleep and high frequency stimulation, to awakening. All the same, different nerve cells may be involved in the two responses. More cannot be said at present.

THE LIMBIC SYSTEM

The cerebral cortex consists of two parts, a phylogenetically older part known as Paleo-cortex and a relatively recent acquisition

the Neo-cortex. The former is mainly concerned with chemical senses and loosely termed as 'rhinencephalon'. But, since the term rhinencephalon is restricted only to those parts in the brain which receive olfactory impulses, there is a necessity for a new term to include in addition to the rhinencephalon, a group of cortical and subcortical structures all of which form a limb or ring round the corpus callosum. The term limbic lobe or system was coined for this purpose.

Components of Limbic system :

1) Paleocortical structures:— Hippocampus, pyriform lobe, olfactory bulb and tubercle.

2) Juxta-allo-cortical structures:— These are situated between the paleo and neo cortex and comprise of cingulate gyrus (limbic cortex) and orbito-insulo-temporal cortex. Other areas are also included.

3) Subcortical structures:— Amygdala, septal nuclei, thalamic and hypothalamic nuclei, caudate nucleus and reticular formation.

Limbic connections and interconnections: These connections have been incompletely worked out.

a) The efferent fibres from the hippocampus and the septal nuclei are connected with the mammillary bodies of the hypothalamus. The fornix which is the main projection from the hippocampus, connects it with various other hypothalamic nuclei.

b) The caudate nucleus receives fibres from the cingulate gyrus and intra-laminar nuclei of thalamus.

c) The reticular formation receives fibres from the hippocampus and cingulate gyrus. Through these connections and other various nonspecific thalamic connections, the paleo and juxta-allo-cortical structures influence a wide area of neo-cortex.

d) The tract of Vicq d' Azyr connects mammillary bodies with the anterior nuclei of the thalamus.

Functions :—

1) The connections between the thalamus and the neocortex which are mainly concerned with the sensory - motor mechanisms, help the animal to adapt itself to the external environment.

2) The hypothalamico-limbic connections are responsible for emotional manifestations. These are also concerned with the repetitive activities related to pleasurable experiences. The neural circuit for this, according to Papez, is

Cortex → hippocampus → Fornix → Mammillary bodies → Mammillo-thalamic tract → Anterior nuclei of thalamus → cingulum → Cortex of cingulate gyrus.

Papez is of the opinion that the central receptive area for emotions is the cingulate gyrus. This view is questioned by others and it appears that no definite function can be attributed to any component of this system in view of conflicting experimental results.

3) The rhinencephalon, which is loosely termed as olfactory cortex and is a part of this limbic system, is concerned with perception of olfactory sensations.

4) The hippocampus is mainly implicated in storing 'recent memory' traces. Bilateral extirpation of this part results in the loss of memory for recent events. Older skilled and learned acts are in no way affected. But in man, recent memory seems to be subserved by not only the hippocampus but also the fornix and mammillary bodies.

5) If the amygdala and pyriform body are destroyed, the animal becomes placid and gradually turns hypersexual in behaviour. So, probably the paleocortical structures which exert an inhibitory action on the subcortical centres in governing sexual activity, may act through amygdala.

Cingulate - Orbito - Insulo - Temporal cortex :

Inhibition of respiration is the obvious feature of stimulation of most of the structures of this ring-like system.

Other regions wherefrom the arrest of respiration is not elicited, are responsible for the so called 'arousal' phenomenon.

Clinical studies of lesions of this system in man, show that the limbic system is very closely concerned with visceral functions.

THE PHYSIOLOGY OF PAIN

Pain, as a symptom of disease, has been of perennial interest to the clinician. Most often, it is a feature which helps the physician to locate the seat of injury or disease, though sometimes it may mislead him if he is none too careful. In the case of trauma, pain causes a withdrawal of the injured part from the noxious stimulus and with regard to pain of a pathological lesion, the patient is made to keep the part still in order to minimise the pain and at the same time avoiding the aggravation and spread of the disease process. Thus, pain is a protective sensation. The bodily adjustments brought about by pain sensation take precedence over other movements, either voluntary or reflex.

Pain is peculiar among the various modalities or kinds of sensations in that, it has the property of 'affect' or emotional quality, (namely that of unpleasantness) in a greater degree than others. As one author has put it, it is difficult to describe it to one who has not felt it. Contrary to what older physiologists thought of it, pain is a separate modality and it is not caused by excessive stimulation of any kind of receptor. It was shown by Adrian and others that intense stimulation of receptors not concerned with pain, could not evoke pain. Pain has a punctate (point-like) distribution on the skin, just like touch, warmth and cold. Henry Head considered pain as a protopathic or a more primitive (from evolutionary point of view) sensation.

Bare or non-myelinated nerve endings seem to be the receptors for pain stimuli. No encapsulated end organs are responsible for pain. These nerve fibres (with cell bodies in the dorsal root ganglion) run to the spinal cord which they enter by the lateral division of the dorsal root and synapse with the cells in the substantia gelatinosa of Rolando and thence are relayed as the lateral spinothalamic tract which in the brain stem forms the spinal fillet and ends in the thalamus. While evidence points to cortical representation of pain sensation, yet stimulation of the

to locate pain
 → end used to interpret
 In 37 cortical skin evokes pain
 cortex plays a role in interpreting
 the quality but not pain sensation

sensory areas in the parietal lobe, does not evoke the pain sensation. The role of the thalamus in the perception of pain is touched upon in the account on it, separately.

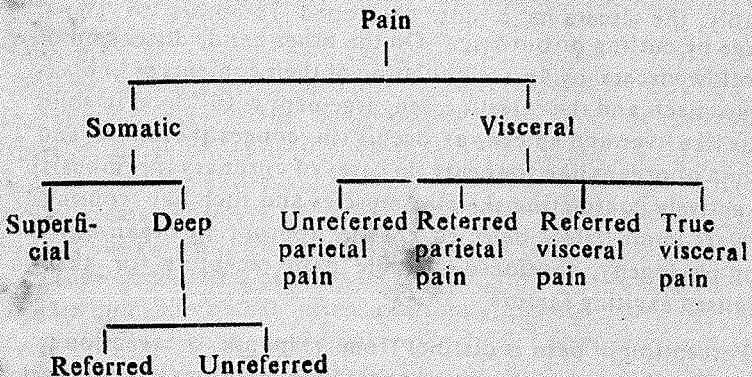
Not all tissues in the body are endowed with pain receptors. Hence, pain can be elicited by injury to only certain tissues like skin, periosteum, parietal layers of pleura and peritoneum, cancellous bone, fibrous capsules of joints, synovial membranes, pelvis of the kidney, the ureter, the base of the urinary bladder, tunica vaginalis of the testis and the urethra. The brain tissue is surprisingly bereft of pain receptors. It can be burnt or cut without causing pain. Most of the viscera can likewise be damaged painlessly. Even the meninges can be similarly subjected to injury, without the occurrence of pain. There is a significance in this. The skin, being the covering of the body, is exposed to a multitude of pain-producing stimuli, while the inner organs are only rarely subject to such noxious excitation. That is why, probably, the viscera have not developed receptors to signal damage by cutting or burning. On the other hand, distension of the hollow viscera by an accumulation of their contents as in bladder, stomach and the intestine, engorgement with blood in solid organs like liver and spleen, as occurs in congestive failure and ischemia of organs like the heart (in cases of coronary thrombosis) or in actively contracting skeletal muscles and such like contingencies are immediately detected in the appropriate organ which during phylogeny, developed suitable pain receptors for these specialised exciting factors.

Perception of pain is distinct from response or reaction to pain. The ability to perceive or appreciate pain may not vary from individual to individual, if this is gauged by determining the threshold strength of painful stimuli. Even psychoneurotic subjects do not differ from normal persons in this regard. The sensitivity to pain (for recognition of pain) may be lowered by certain factors like a placebo or a harmless drug, distraction by other stimuli and by pain in other situations in the body. Counter-irritants like menthol and methyl salicylate act by producing a cooling or chilling effect and thereby raising the threshold. It is in the degree or intensity of response that there seems to be appreciable differences among people. Psychoneurotics are marked in their reaction to pain. The reaction to pain

may be of different types in the same person, under different circumstances. Athletes engrossed in sports and games (football players engaged in a very exciting game) may not even be conscious of injuries sustained during their activity. Soldiers on the battlefield may ignore even severe injuries when fighting in a determined manner. Certain individuals by training or by nature, react very mildly to pain and these are known as stoics.

Some of the reactions to pain are seen as:- withdrawal of the affected part or keeping it still, autonomic effects like rise or fall in the blood pressure, vasomotor tone, heart rate and respiration.

Classification of pain:- Various sub-categories of pain have been described, based on several criteria. A fairly comprehensive scheme is as follows:—



Superficial somatic pain is caused by injury to the skin. It is usually designated as cutting, burning and pricking pain, depending on the nature of injury. Superficial pain as caused by a pin prick, is also called as bright pain, probably since it can be described fairly accurately and can be localised with some degree of precision. There is no sensory adaptation to pain of any category, nor summation is seen with regards to weak stimuli applied away from each other.

Fast and slow pain: When a nocuous stimulus is applied to the skin, as with a pin, in the very beginning, the contact

of the point of the pin with the skin is felt as a touch sensation. This is due to the faster conducting touch fibres. Next, a sharp pain is caused and this sensation is mediated by relatively faster conducting pain fibres of the 'A δ ' class of nerve fibres. This ceases very soon and is replaced by a long lasting and more severe pain which is due to conduction along non-medullated 'C' type fibres.

The intensity of pain sensation has been graded and about twenty degrees of pain are said to exist. This has been achieved by using radiant heat from a high powered electric bulb. The pain unit is called *Dol*.

Fast pain is protective in its function. In *Tabes-dorsalis*, it is the fast pain that is abolished, slow type being retained. Pain sensations disappear last, after injuries to nervous system, as well as when the depth of anaesthesia is gradually increased.

Deep Pain: This sensation can be elicited from muscles, bones and joints. It is not accurately localised and is said to be dull or sickening or aching in character. Associated autonomic responses are more commonly seen along with deep pain. The pain of ischaemic muscle which is aggravated by exercising it, is thought to be due to the release of an unknown 'P' substance (so called, by Lewis). This chemical agent may most probably be potassium ions which escape out of the muscle fibres during contraction and excite the pain fibres.

Hyperalgesia: When an injury occurs, soon after, in the injured area the skin becomes abnormally reactive to painful stimuli. The sensation caused by this is intense and of a burning nature. Such a condition is called hyperalgesia. In the primary form of hyperalgesia, the threshold for stimulation is lowered, the skin appears red, histamine is thought to be released at the site of injury and it diffuses into the neighbouring tissues, producing pain (by exciting nerve fibres and vaso dilatation). Lewis doubted the identity of the chemical factor, because itching was not produced. In secondary hyperalgesia, there is actually a raising of the threshold. The sensation caused is abnormally unpleasant and so it is called hyperpathia. The area of skin

affected is not confined to the site of injury but is much wider, but this condition does not last longer than 48 hours whereas primary hyperalgesia lasts for days. There is a latency in the development of secondary hyperalgesia.

Lewis was of the opinion that in the case of hyperalgesia, a separate system of nerve fibres (nocifensor fibres) was excited; but recent evidence does not support his conclusion. The same non-myelinated pain fibres are responsible for this also.

Referred somatic pain: Pain caused in a deeply hidden somatic structure, like a joint, may be felt in another part of the body, for e.g. — in tuberculosis of the hip, pain is experienced not in the hip region but in the knee region. The basis of referred pain is dealt with under 'Visceral pain'.

Visceral Pain: The problem of visceral pain looms large in the minds of both the clinician as well as the physiologist. When the viscera which are deep inside the body cavities suffer pathological changes, unlike in the case of cutaneous pain, the localisation of the seat of pain is sometimes very difficult. Visceral pain is conveniently considered under four categories.

a) *Unreferred Parietal pain:* Whenever an inflamed viscus comes into contact with the parietal layer of the serous membrane lining the cavity containing the viscus, pain is localised in the body wall just external to the point of contact. Appendicular pain is thus felt in the lower right quadrant of the abdomen. Of the serous membranes lining the body cavities, it is only the parietal layers that are endowed with pain sensitive terminals.

b) *Referred Parietal pain:* Pain of sub-diaphragmatic abscess in the region of the central zone of the diaphragm is referred to the point of the shoulder and neck. The part of the diaphragm concerned and the shoulder region are both innervated by spinal nerves arising from C₃ and C₄ segments of the cord. Likewise, pain due to irritation of the edges of the diaphragm is referred to the anterior wall of the abdomen, both being innervated by the lower six intercostal nerves.

c) *Referred Visceral Pain:* Pathological lesions in viscera excite afferent nerves in them, usually belonging to the sympathetic system. But the pain caused by such lesions is referred in each

case, to a particular region on the body surface. There are quite a number of examples well-known to clinicians and which are useful in accurate diagnosis. The pain of angina pectoris and of myocardial infarction is the most well-known of these. It is referred to the left shoulder and even radiates down the left arm. The pain of appendicitis is referred in the initial stages, to the umbilical region.

d) *Unreferred or True Visceral Pain*: This is also known as True Splanchnic Pain. While the pain of myocardial ischaemia or infarction is referred to the left shoulder and the left arm, it is also felt behind the sternum (retrosternal pain). The afflicted subject feels that the pain is in the heart region. Labour pains, as occur during uterine contractions, are felt by the patient, to arise deep in the abdomen – that is, from the uterus. The pain of peptic ulcer seeming to be in gastric region deep inside the abdomen, is another example of true visceral pain.

Just as an injured limb is withdrawn to protect it from further injury and the limb is kept immobile to avoid pain, visceral pain also evokes reflex muscle contraction. In the case of intra-abdominal lesions, the abdominal wall is kept in a rigid condition (guarding) to protect the inner parts from further injury. Such reflexes, whether they occur in the limbs or in the abdominal muscles or elsewhere, are called Nociceptor Reflexes.

Afferent fibres from Viscera: For some years, it was held that the autonomic nervous system comprised only efferent or motor fibres. The existence of sensory afferent fibres has been recognised relatively recently. The course of afferent pain fibres from the interior of the body as well as from various viscera seems to be through the parasympathetic or the sympathetic system depending on the region of the body in which the viscus lies. Thus, pain fibres from all inner organs, above (rostral or superior to) what is known as the thoracic pain line which roughly passes through the cardiac end of the oesophagus and the point of bifurcation of the trachea, are routed through parasympathetic nerves which ultimately enter the spinal cord through the dorsal roots. Likewise, all organs which are anatomically inferior (caudal) to the pelvic pain line passing through the pelvic colon

as well as the cervix of the uterus and the lower part of the urinary bladder, have their pain fibres channelled through parasympathetic nerves. The pain fibres from all organs lying below the thoracic pain line but above the pelvic line, travel along with sympathetic nerves to gain entry into the spinal cord through the dorsal roots.

The mechanism underlying referred pain is still to be elucidated satisfactorily. Two views have held the field. According to Mackenzie, each viscus and certain surface areas of the body (dermatomes) discharge impulses to the same spinal neurones through the same spinal roots. When the former send impulses to the spinal neurones, the effect of the impulses arising from cutaneous receptors and arriving at the spinal neurones is facilitated. Otherwise, the impulses of cutaneous origin will not activate the spinal neurones. The visceral impulses as such cannot be relayed to the higher centres since the visceral afferents are assumed not to have direct connections with higher levels in the sensory pathways, to which only cutaneous afferents can signal information. Hence visceral pain is 'felt' in superficial areas. This explanation goes by the name "Convergence Facilitation Theory". A rival view, known as the "Convergence Projection Theory" explains the occurrence of referred pain as follows - Pain impulses generated in internal organs ascend up to the sensory cortex through the usual pain pathway but, since the sensorium has not been trained from birth to locate the seat of trouble in deep organs, such pain is projected to a point on the body surface which falls within the dermatome sharing the same sensory neurones in the cord and hence the same dorsal root as the affected organ. It is not facilitation of cutaneous impulses that occurs but 'erroneous' projection that takes place. It is not possible to choose between the two view points, as either has satisfactory evidence in its favour.

In the case of unreferred parietal pain, the sensation is projected to that part of the parietal serous membrane where the sensory nerves are excited by contact with an affected organ. This of course is not really a case of "referred" pain.

Habit reference: It sometimes happens that the site to which pain is referred may alter under special conditions. In

subjects who have undergone surgery, pain arising from distension of hollow viscera, is referred to the site of the surgical scar. This is an example of an aberrant projection. Similar to this is the case of pain referred to the teeth from neighbouring air sinuses, in subjects who have had dental operations.

In a neurological condition known as Syringomyelia, pain and thermal sensations are lost while touch is retained. This is due to the progressive gliosis of the spinal cord in the neighbourhood of lateral spinothalamic tract, causing compression of the pain fibres. In this condition as well as in another known as Tabes Dorsalis, in which pain sensation is either blunted or lost, the patient is unable to protect his extremities and other parts of the body from repeated injury. Leprosy is another well known condition in which there is a severe loss of the pain sensation, due to neuritis. The absence of pain exposes the individual to repeated trauma.

THE CEREBRO-SPINAL FLUID

The brain and the spinal cord are enclosed by three membranes which are called collectively as the meninges, named from without inwards as the dura-mater, the arachnoid and the pia-mater. The dura is itself double layered, the outer one being called the periosteal layer and the inner one, the meningeal layer. The cerebral venous sinuses are found in between the two dural layers. The structures known as arachnoid villi formed by the arachnoid, pierce through the meningeal layer of the duramater and project into the venous sinuses. The villi are the main channels by which the cerebrospinal fluid is absorbed into the venous blood. The arachnoid is a web-like membrane which bridges across all the sulci of the brain (excepting the longitudinal fissure). The pia mater is very delicate and is closely adherent to the brain matter and it dips into the sulci and is carried as a tube-like covering for each cerebral vessel as it enters the parenchyma of the brain and thus, there are extensions of the perivascular spaces upto the nerve cells. The space between the arachnoid and the pia is known as the sub-arachnoid space and it contains the cerebrospinal fluid. The subarachnoid space continues along the course of spinal and cranial nerves which are invested by the two inner meninges. The

optic nerve shows these most typically. In certain regions, the sub-arachnoid space widens out to form cisterna - the cisterna magna between the medulla and the cerebellum, the cisterna pontis on the under surface of the pons and the cisterna interpeduncularis in the space between the tips of the temporal lobes at the base of brain. The subarachnoid space of the brain is continuous with that of the spinal cord. Since the dura and the arachnoid reach as far as the second sacral 'vertebra' and the spinal cord has its lower end at the lower border of the first lumbar vertebra, the cerebrospinal fluid can be tapped by puncturing the subarachnoid space below the end of the spinal cord without injuring the cord, the cauda equina never suffering an injury in this procedure. The central canal of the spinal cord opens at its upper end into the fourth ventricle.

Site of formation of the cerebrospinal fluid (C.S.F.): The plexuses of blood capillaries found in the walls of the cerebral ventricles, known as the choroid plexuses, are considered to be the major site of formation (see below for subsidiary sources) of the cerebrospinal fluid. The evidence for this conclusion is as follows:

- 1) C. S. F. flows out continuously through a cannula inserted into any ventricle.
- 2) An obstruction to the circulation of the CSF leads to distension of the ventricles, which state is known as hydrocephalus. If the choroid plexus is excised prior to the setting up of the obstruction, hydrocephalus does not develop.

A subsidiary source of CSF formation are the perivascular spaces - Virchow-Robin's space - which are extensions of the sub-arachnoid space (see above). The cerebrospinal fluid is also reabsorbed to some extent, here.

Most of the absorption is through the arachnoid villi into the cerebral venous sinuses.

Composition and mode of formation of CSF: Apparently this fluid looks like an ultrafiltrate of the plasma. Yet, certain discrepancies in its concentration in relation to plasma, cast a

doubt on this mechanism being the basis of the formation of the cerebrospinal fluid.

The quantity of the cerebrospinal fluid is not known with certainty, though it is estimated to be about 120 ml. (a cupful, as one author puts it) and it exerts a pressure of about 150 mm. of water in the lying position with a cannula piercing the subarchnoid space in the lumbar region. It rises to about 280 mm. in the sitting posture and very much higher while standing. Even these values vary very much. Manual compression of the neck raises the pressure—Queckenstedt's sign is a clinical test for detection of obstructions in any part of the CSF space. CSF is colourless and clear and of nearly the same pH as blood and has a specific gravity of 1005. It contains no red cells and lymphocytes are the only white cells present and that too in very small numbers—5 cells per cubic mm. The protein content is very low, 0.04% in the lower spinal region. It is still lower in the ventricles. The compositions of plasma and CSF when compared are as follows:

	Plasma (%)	Cerebrospinal fluid (%)
Plasma proteins	7— 8 gms	20— 30 mg.
Urea	15— 35 mg	10— 40 mg.
glucose	70—100 mg	50— 80 mg.
sodium	320—340 mg	350 mg.
potassium	15— 20 mg	8 mg.
calcium	10 mg	5 mg.
chloride	360—380 mg	440—455 mg.
Bicarbonate as CO ₂	50— 75 vols	50— 75 vols
Inorganic phosphate	2— 5 mg	1— 2 mg.

The greater amounts of sodium and chloride in the cerebrospinal fluid can be explained only on the basis of active secretory process involving a sodium pump which brings about osmotic disturbances and hence a passive movement of water. A passive ultra-filtration process cannot be thought of as a sole mechanism, because the ionic distribution between the plasma and the cerebrospinal fluid does not conform to Donnan's equilibrium.

Circulation of CSF: The fluid which is formed in each of the lateral ventricles, enters the third ventricle through the foramen of Munro and mixes with the fluid formed in the 3rd ventricle. The fluid next passes on to the IV ventricle through the aqueduct of Sylvius. Drainage from the IV ventricle is through the central foramen of Magendie and the lateral ones of Luschka, to gain access to the subarachnoid Cisterna Magna. A little of the fluid passes down the spinal subarachnoid space, with some absorption taking place. It returns to the cerebral subarachnoid space. Most of the fluid bathes the entire cerebral hemispheres by passing through the cisterns at the base of the brain and spreading over the lateral surfaces of the hemispheres and the cerebellum. It is absorbed into the dural venous sinuses through the arachnoid villi.

Functions of the CSF: The brain is suspended inside the skull by blood vessels, nerve roots and innumerable fine fibrous strands (arachnoid trabeculae). It is surrounded on all sides by the CSF which supports it as if on a cushion of fluid. This buffer action of the CSF provides protection to the delicate and semi-solid brain matter, from blows or mechanical shocks and jolts to the head.

Secondly, in view of the rigidity and non-yielding nature of the skull, CSF provides a safety valve when the intracranial pressure rises on any account (tumor). In such a contingency, the volume of the CSF is diminished to allow for a rise in intracranial pressure which thus is compensated for. The adequacy of blood supply is ensured by this means.

Lumbar puncture: A sample of the CSF is most easily obtained for diagnostic purposes, by tapping the spinal subarachnoid space between the 4th and 5th lumbar vertebrae. By this means, the pressure of the CSF can also be determined. The long hollow needle whose tip enters the subarachnoid space, is connected to a water manometer, to read the pressure. Lumbar puncture is also resorted to, to reduce intracranial tension, as in meningitis; or to introduce drugs like anaesthetic agents for spinal anaesthesia and also bactericidal agents, like antibiotics. With a hollow needle in the spinal subarachnoid space, when digital pressure

is applied to the jugular veins in the neck in normal subjects, CSF flows out through the needle at a faster rate (Queckenstedt's sign).

Loculation Syndrome: (Froin syndrome) - A neoplastic growth, say, of the spinal cord or of the tissues surrounding it, causes certain qualitative changes in the cerebrospinal fluid held distal to the growth. The protein content is increased and there is a yellow discoloration of the fluid, caused by the stasis of blood in the spinal veins and consequent haemolysis, with the derivatives of haemoglobin diffusing into the CSF. Plasma carotene also contributes to the yellow colour. Queckenstedt's sign will be negative, if the obstruction is above the lumbar region.

Hydrocephalus: This is an excessive accumulation of cerebrospinal fluid in the ventricles or subarachnoid space, because of greater rate of secretion or obstruction to flow or diminished absorption. The great pressure exerted on the brain tissue in this condition, leads to its destruction. Even the skull may be enlarged in size, especially in babies.

Ventriculography: Air can be injected into the ventricles after trephining the skull and passing a long hollow needle through the prefrontal lobe, into a ventricle. X-ray photographs of the head are taken in the anteroposterior and lateral views. The shape of the cerebral ventricles can be visualised by this procedure.

Blood-brain barrier: In animals, when certain dyes like trypan blue were injected intravenously, it was found that nearly all organs and tissues were intravitaly stained, excepting the nervous tissue. This showed that the dye could not reach nerve cells, probably because of a barrier between the blood and the nerve cells. It is this barrier that determines, to a large extent, the composition of the CSF. Very little protein can enter CSF. Lipid solubility enables certain substances to leave blood for CSF, though this is not always so. Even pH may not be a decisive factor. The cerebral capillaries are permeable to bile pigments at birth, but not in the adult. While there are gaps between the endothelial cells in the walls of capillaries of the choroid plexus, there are none in the case of brain capillaries which are covered

completely by a basement membrane, outside which are astrocytes whose end feet cover over 85% of the basement membrane. These structures may constitute the blood-brain barrier.

This barrier possibly helps to maintain the immediate environment of the brain cells in an unchanging state, so that their functions can be discharged efficiently. Clinically, it is known that certain therapeutic substances – antibiotics like penicillin and chloramphenicol, do not reach the brain tissue when administered parenterally. Sulphonamide compounds, however, may be able to have access. The physician has to use only such agents that can penetrate the barrier. Certain parts like the posterior pituitary gland, seem to be unaffected by the presence of the barrier.

THE AUTONOMIC NERVOUS SYSTEM

This term refers to that part of the nervous system which controls those bodily activities or processes which are not under voluntary or volitional control. Alternative terms are vegetative or involuntary nervous system. Feldberg, a well known authority in this field, is not happy with the term 'involuntary', since even spinal reflexes are involuntary though mediated by somatic nerves of the so called voluntary system of fibres. On the other hand, some subjects are even able to voluntarily raise or lower the heart rate or change the level of activity of some organ. These effects are usually considered to be beyond voluntary control. Anyway, to differentiate this system of fibres from the rest of the nervous system, it was described as made up of the efferent fibres which arose from cells in the lower brain stem (pons and medulla), as well as certain segments of the spinal cord namely the thoracic and lumbar and the sacral, and eventually innervate the secretory cells of the various glands and smooth muscles of the viscera, blood vessels and the heart. This definition itself is not quite valid, since it excludes the afferent fibres of the viscera and other structures which subserve the visceral sensations, including visceral pain. In the present discussion, the afferent fibres have been excluded, since their role in visceral pain and other visceral sensations are dealt with elsewhere.

The autonomic nervous system consists of two parts – the sympathetic and the parasympathetic divisions. The fibres of either division conform to a general plan or anatomical arrangement. The terms used in this connexion, owe their inception to Langley and Dickinson who used nicotine in locating the positions of ganglia in the autonomic system and thereby revealed the pathways or the courses which the nerve fibres took in gaining access to their effector tissues or organs. The preganglionic fibres arise from nerve cells which are situated in 1) certain cranial nerve nuclei – those of the 3rd, 7th, 9th, and 10th. (cranial outflow of parasympathetic system); 2) the lateral horns of the thoracic and lumbar spinal segments (T_1 to L_2) forming the sympathetic outflow; 3) the lateral region of the grey matter of the 2nd and 3rd sacral spinal segments (sacral outflow of the parasympathetic system). These fibres leave the central nervous system through– 1) the cranial nerves and 2) the motor roots of the spinal cord. In the case of the sympathetic fibres, the anterior roots giving rise to the spinal nerves T_1 to L_2 convey the autonomic fibres over a short distance, beyond which they separate out to form the white rami communicantes (white – myelinated) which terminate at or pass through the ganglia of the paravertebral sympathetic chain. The nerve cells which provide the relay for the preganglionic fibres, by means of post ganglionic fibres arising from them, are found in:— 1) the paravertebral chain of sympathetic ganglia, 2) the collateral or prevertebral ganglia & 3) terminal ganglia. Sympathetic fibres are relayed mostly in the vertebral ganglia and those fibres which pass through these ganglia without interruption, end in the collateral ganglia, but rarely or not at all in the terminal ganglia. The preganglionic parasympathetic fibres end in the terminal ganglia which occur either very close to or in the substance of the effector organs themselves. It follows from the foregoing description that while the preganglionic fibres are short compared to the postganglionic fibres, in the sympathetic system, the reverse is the position in the parasympathetic division. There is one more consequence of this arrangement. It has been estimated that each preganglionic fibre of the sympathetic system, makes contact with at least 20 neurones in the ganglion where it ends, and thereby the effects of excitation of preganglionic fibres is very widespread. On the contrary, parasympathetic effects are

very much confined or localised to a single organ or a circumscribed region of the body. This fact is of great physiological significance.

Sympathetic system:— The term, sympathetic, is of ancient coinage. Galen, the Greek physician of Rome, conceived of the notion that sympathy or consent between various parts of the body, was generated by the action of these nerve fibres. The lateral horn cells of the spinal segments (see above), receive fibres from the various medullary centres (respiratory, vasomotor, cardiac etc.) and from the hypothalamic autonomic centres. Most of their axons emerge from the spinal cord through the motor roots and pass on to the vertebral chain of ganglia (B group of myelinated fibres) through the white rami communicans. The majority of the fibres arising from one spinal segment, end in the ganglion corresponding to the spinal segment. An appreciable number either ascend or descend in the chain of ganglia to terminate in a ganglion above or below. The three cervical ganglia - superior, middle, and inferior - receive fibres which have their origin in the thoracic spinal segments and after entering the ganglia opposite to them, ascend up. In man, the inferior cervical sympathetic ganglion is fused with the first thoracic ganglion and it is known as the stellate ganglion. The non-myelinated fibres (C group) which arise in the sympathetic chain of ganglia, either pass through the peri-arterial plexuses to reach their final destination, especially in the case of sympathetic fibres to the blood vessels, glands and organs in the head and neck which are conveyed by the periarterial plexus of the carotid arteries or leave the sympathetic chain and join the spinal nerves by means of the grey rami communicans and finally find their way through the somatic nerves to their effector tissues. The sympathetic preganglionic fibres from the spinal segments between T_6 and T_{12} which are meant to innervate abdominal organs, do not synapse in the lateral sympathetic chain but after passing through it, end in the collateral or prevertebral ganglia such as the coeliac (semilunar), superior mesenteric, renal, spermatic and ovarian ganglia, forming the greater splanchnic nerves. Others, having their origin in L_1 and L_2 segments and forming the presacral nerve in man, establish contact with the hypogastric ganglia, to finally innervate the rectum and the

bladder. The post ganglionic fibres of the collateral ganglia mentioned above, travel along the walls of the large arteries, to innervate their walls as well as the organs of the abdomen. The adrenal medulla which, embryologically, is homologous with the paravertebral ganglia, receives fibres directly from the spinal segments ($T_5 - T_9$) which reach the gland by passing through the coeliac ganglia without synapsing in it and running in the splanchnic nerves.

More details regarding the origin and distribution of sympathetic fibres to various parts of the body and the various organs as well as their actions on them, are given in the relevant chapters dealing with different functional systems of the body. One point only needs to be stressed — that a preganglionic sympathetic fibre makes synaptic contacts with cells in different ganglia and so, stimulation of such a fibre has widespread effects.

Certain organs have only sympathetic innervation. These are the arrectores pilorum muscles of the hair follicles. On the other hand, the glands of the stomach and pancreas may have only parasympathetic supply.

Parasympathetic system: As mentioned already, there is an outflow of fibres in the cranial nerves 3, 7, 9 and 10. The vagus is the most prominent of the parasympathetic nerves with widespread ramifications of its branches reaching quite a number of organs, the farthest branches being given off to the transverse colon. The details as regards the organs and structures innervated by these, are presented in appropriate contexts. The sacral outflow arises from the cells in the lateral region of the spinal grey matter of S_2 and S_3 spinal segments. The preganglionic fibres, after leaving the cord, enter the pelvic ganglia, from which emerge the post ganglionic fibres which innervate the plain muscles of colon, bladder and the uterus.

The role of chemical transmitters] in the autonomic nervous system: The simple and classical experiments of Otto Loewi (1921), wherein he perfused two frog's hearts, the perfusing fluid passing into one heart was siphoned into the second. When the vagus nerve to the first heart was stimulated resulting in its arrest, the second heart also was inhibited when the outflow from

Parasympathetic System

Sympathetic System

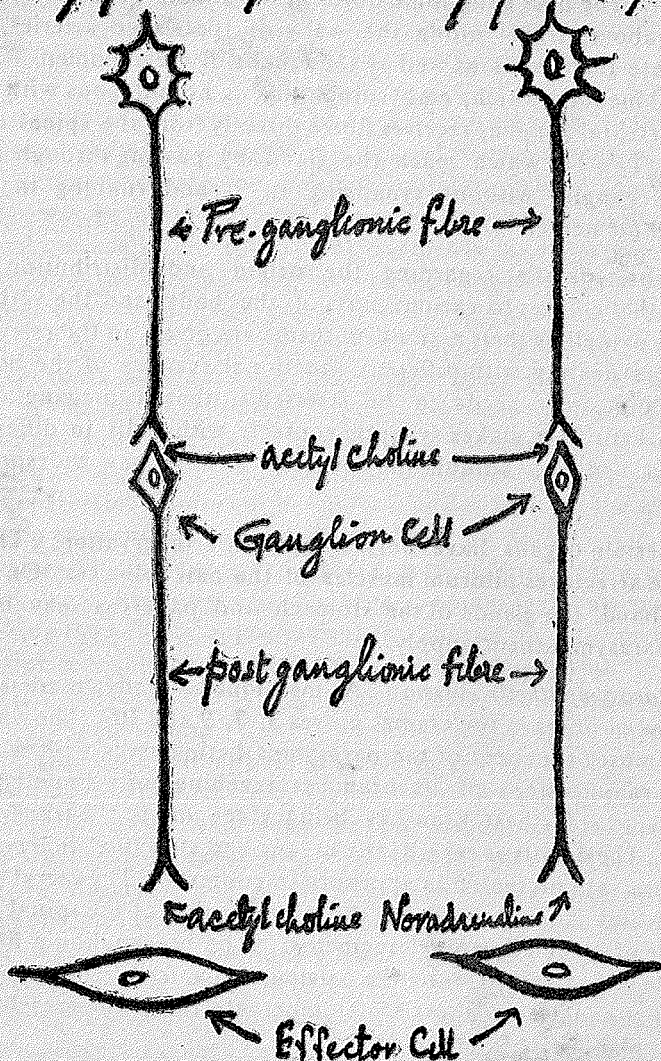


Fig. 62

the first entered the second heart. This fact demonstrated the release of an unknown humoral agent in the first heart as a consequence of vagal excitation. This was given the name of Vagus Stoff which later on was identified as acetyl

choline, by Dale. Subsequently Dale, Brown and Feldberg showed that, acetyl choline was a chemical transmitter at the neuromuscular junction. Loewi was awarded the Nobel prize for his epoch making discovery. He showed that, similarly, another transmitter was released on stimulation of sympathetic fibres to the heart and this was named accelerans substance because of its action on the heart. Cannon referred to it as sympathin. Since sympathin had an excitatory effect at certain sites and an inhibitory action at others, it was postulated that there were two sympathins - sympathin E (excitatory) and sympathin I (inhibitory). Later work revealed that the former is noradrenaline and the latter adrenaline. It is now established that only noradrenaline is the chemical agent released at the postganglionic terminals of the sympathetic system. The accompanying figure (Fig. 62) depicts the release of the transmitters in the two divisions of the autonomic nervous system.

It is to be noted that acetylcholine is released at the terminals of the preganglionic fibres of both the parasympathetic and the sympathetic systems. It is only at the endings of the postganglionic fibres, that the transmitters are different. Even so there are exceptions in the case of the sympathetic system Acetyl choline is liberated at the postganlionic terminations in the case of sympathetic fibres to the sweat glands and the arrectores pilorum muscles. The terms, cholinergic and adrenergic, indicate which transmitter is set free at the terminals of a fibre. Acetylcholine is the humoral transmitter at the terminals of the splanchnic nerve fibres which are to be considered anatomically as preganglionic, ending on the secretory cells of the adrenal medulla. It is interesting to note that the released acetylcholine acts on the adrenal medullary cells and makes them liberate adrenaline and noradrenaline whose pharmacological actions are opposed to those of acetyl choline.

A reference has already been made to Langley's use of nicotine in establishing the presence of ganglia interposed in the pathways of autonomic fibres. Nicotine, which is an alkaloid of tobacco, when painted over expected locations of ganglionic cells, initially excites the postganglionic neurones which discharge impulses into their axons, but later, causes a block at the

synapse between the preganglionic fibre and the ganglion cell, by producing a state of depolarisation of the post-synaptic membrane. Nicotine is a naturally occurring substance and is the first of the large group of ganglion - blocking agents, of which there are many synthetic ones in therapeutic use. The pleasure of smoking, if one can consider it so, lies in the preliminary excitation of the postganglionic neurone (the initial action of nicotine) bringing in its wake motility of the gut and such effects of autonomic hyperactivity.

In the parasympathetic system, acetylcholine is liberated both at the ganglionic synapse, as well as at the effector cell, be it glandular or plain muscle. The former is known as the nicotine action, since acetylcholine causes the discharge of the ganglionic nerve cell, just as in the case of the initial action of nicotine (see previous paragraph). This nicotine action of acetyl choline is blocked by nicotine itself. The effect of acetylcholine on the plain muscle or glandular cell is referred to as the muscarine action. Muscarine is a parasympathomimetic (mimetic - that which mimics or imitates something else) drug, derived from mushrooms. This type of action is abolished by atropine, an alkaloid of Belladonna, the deadly nightshade plant. The mode of action of atropine is that of a competitive inhibition in which atropine occupies the 'receptor sites' on the effector cell and thereby renders acetylcholine ineffective. Ergotoxine and ergometrine are the antagonists to adrenaline and these act in the same way as atropine in respect of acetyl choline.

The functions of the Autonomic Nervous System: Claude Bernard, the famous French Physiologist of the last century, spoke of a proper environment by which all the tissues were surrounded and which enabled them to discharge their various functions at an optimum level. To this environment which is the extracellular fluid bathing the cells of the body, he gave the name milieu interieur or milieu interne, which has to be maintained in an unchanging or constant state, as regards its physical and chemical characteristics. Walter Bradford Cannon, an American physiologist, termed all the processes aimed at preventing changes in the internal environment, or maintaining its constancy as homeostasis.

Two physiological control systems exist in the body, which are primarily concerned with homeostasis – namely – the endocrines and the nervous system. The role of the endocrinal control of the milieu interieur is discussed separately. The nervous system is composed of the so called somatic nerves (concerned with activity of the skeletal or voluntary muscles) and the autonomic nerves which regulate the activity of plain muscle and exocrine glands, like those of the alimentary tract and sweat glands. The autonomic nervous system possibly is concerned with the proper functioning of even the endocrines, though this aspect has yet to be worked out more satisfactorily.

Of the two, the sympathetic division acts under provocation of a sudden change, physical or chemical, in the external or internal environment. A change in the external environment, if unchecked, leads to an upsetting of the internal environment. A fall in the temperature of surroundings brings on the heat conservation mechanisms like piloerection (hairs standing on end), shivering and cutaneous vasoconstriction. A fall in the blood sugar level, provokes sympathetic nervous activity, leading on to the release of adrenaline from the adrenal medulla which promotes glycogenolysis and restores the blood sugar content to the original or normal level. When an animal's existence is threatened by a predator or rival, the flight (in the former instance) or the fight response (latter case) is manifested. All autonomic reactions necessary to improve the efficiency of the skeletal muscles, in order to run away from the enemy or fight the competitor, are brought into operation. The heart beats faster and more powerfully, improving the blood supply to the active muscles. The blood is diverted from idle or less vital regions to the active muscles, on account of the vasomotor activity – vasoconstriction in cutaneous and splanchnic vessels and dilatation in the muscles. Respiration is adjusted to furnish more of the required oxygen to the needy muscles – the rate and depth of breathing are increased. Liver glycogen is rapidly broken down to replenish the 'fuel' for the contracting muscles. In all these changes, the adrenal medulla is actively involved along with the sympathetic nerves. Hence, it is customary to talk of a sympathico-adrenal system, whose excitation brings

about a widespread or diffuse state of heightened activity which depletes the body reserves of energy.

In contrast, the parasympathetic nerves are responsible for changes which are confined to one organ or the other. This activity is directed to restore the body reserves. For example, the vagus promotes the secretion of digestive enzymes. It also promotes movements of the alimentary canal, so necessary for digestion and even more important for absorption of the products of digestion which are used to build up the stores of materials in the body. Vagal stimulation slows down the heart, reducing its work load. (It is in this regard that Gaskell applied the terms, anabolic and catabolic nerves, to the parasympathetic and sympathetic fibres respectively). Vagal stimulation increases the glycogen stores of the liver, since insulin is secreted in response to it.

In the light of many opposite effects caused by the sympathetic and the parasympathetic nerves, it has been held that these two divisions are mutually antagonistic in action. This certainly holds good in several instances. Vagus is cardio-inhibitory, while the sympathetic nerves are cardio-acceleratory. Parasympathetic action results in emptying of the urinary bladder, whereas filling of the bladder is promoted by sympathetic excitation. Alimentary canal movements are intensified by the former, while these are depressed by the latter. Yet, in certain instances, as for example salivary secretion, both sets of fibres are excitatory to the salivary glands, the chemical nature of secretion however being different in the two cases.

Sympathetectomy or removal of sympathetic fibres is resorted to in certain clinical conditions like thromboangitis obliterans, as a therapeutic measure to relieve vascular spasm and improve the blood supply to the extremities. Patients who undergo such surgery do not exhibit any untoward effects. In fact, the sympathico adrenal system is really not essential for the maintenance of life. Such subjects can lead normal lives, provided they are not exposed to stress. So long as they can lead placid and quiet lives, all can be well with them for all practical purposes.

It remains to explain certain commonly used terms in regard of autonomic effects, especially pertaining to the drugs affecting this system of nerves.

Sympathomimetic agents – those drugs whose action is the same or similar to that of the sympathico-adrenal system, eg.—adrenaline and noradrenaline.

Sympatholytic agents – These which annul the effects of sympathetic excitatton or of the sympathometic drugs were originally obtained from ergot – ergotoxine. A number of synthetic substitutes like dibenamine, dibenzylamine and guanethidine have come into use recently.

Parasympathomimetic substances—acetylcholine was the first to be discovered. Others are pilocarpine and carbaminoylcholine. Eserine and prostigmine augment the action of acetylcholine.

Parasympatholytic drugs—These belong to atropine group of drugs. They minimise or abolish parasympathetic effects.

THE PHYSIOLOGY OF THE SPECIAL SENSE ORGANS

Vision, audition, gustation (taste) and olfaction (smell) are conventionally considered as special senses, because each one of these has a special area in the cerebral cortex devoted to it. In the case of taste, this statement is not quite valid since the cortical centre for it, is located in the lowest portion of the somesthetic area itself. Further, the end organs for the special senses are all found in the head itself and not in the rest of the body, as is the case with general senses like touch, pain, warmth and cold. Some authors used to include touch also under special senses though the reason for this is not apparent and such a practice is likely to render the term 'special senses' meaningless.

THE EYE

The eye is the most complex, structurally and functionally, of all the end organs. The ear and the muscle spindle are only slightly less complicated though they also are highly organised in their structure. The eye, phylogenetically, has evolved over a very long time and all the functional aspects of the eye have yet to be satisfactorily elucidated.

Protective devices for the eye: a) The eyeball (globe) is situated in the bony orbital cavity formed superiorly by the orbital plate of the frontal bone as the roof, the roof of the maxillary sinus (of maxilla) forming the floor, the lachrymal bone and the orbital plate of the ethmoid in the medial wall and the orbital surface of the zygomatic bone and the greater wing of the sphenoid in the lateral wall.

b) There are two eyelids – the upper and the lower – which can cover the exposed anterior aspect of the eye, including the cornea, when required. When the eyelids are kept open, the gap between them is called the palpebral fissure. Of the two, the upper eyelid is larger in area, of greater length and is more mobile in its movements than the lower. At the free edges of the two lids are present short and stiff hairs, the eye lashes. The

two lids have the same histological features except that the upper one has an extra muscle, the levator palpebrae superioris, responsible for its elevation. The tissues that occur in each eyelid are, from without inwards – skin, subcutaneous tissue, orbicularis oculi, the tarsus, the orbital septum, tarsal glands and the conjunctiva. In the upper lid, the fibres of the levator are found deeper (posterior) to the orbicularis. The tarsus is a fibrous plate which is responsible for the curved shape of the eyelid. The orbital septum is a weak membranous sheet attached to the edge of the bony orbital cavity and it merges with the aponeurosis of the levator at the free edge of the lid. The tarsal glands are analogous to the sebaceous glands of the skin.

The movements of eye lids, by closing and opening the eyes, regulate the amount of light entering the eyes. They protect the eyes from excessive light and foreign bodies, and spread lachrymal secretion over the exposed part of the eye and prevent their drying up. The orbicularis oculi closes the eye and levator palpebrae superioris raises the upper lid. When one contracts, the other relaxes. In sleep, the levator is relaxed and the orbicularis is in tonic contraction. While the subject is awake, the levator is tonically contracted and orbicularis relaxed. The orbicularis is supplied by the facial nerve and sympathetic fibres. The levator is supplied by the oculomotor and parasympathetic nerve fibres.

Movements of eye lids: a) When the head and eyes are lifted upwards, the levator contracts.

- b) On closing the eye lids, the pupil contracts and the eye ball is rotated upward and outward.
- c) The eye lids of both eyes move in the same direction and determine facial expression.

Blinking movements: 1) Voluntary blinking – the eye cannot be kept open at a stretch. Closure of the eye occurs now and then 2) Reflex blinking – external stimuli like bright light, loud noise and touching the eye or the conjunctiva, provoke the reflex. 3) Spontaneous blinking – This occurs very frequently – rhythmic closing and opening 10-20 times per minute. Tears

are spread over the eye by this means. A single movement takes 0.4 sec. Its cause is unknown.

LACHRYMAL SECRETION

The chief lachrymal gland is in the superolateral part of the orbit in a fossa in the bony roof and smaller glands are also seen along the fundus of conjunctiva. Irritation of the nasal mucosa or of the conjunctiva, causes tear secretion. The afferent impulses pass through the V nerve. Lachrymation is also associated with vomiting, sneezing and coughing and due to psychic causes sorrow or hilarity. In actors, it may be seen as a conditioned reflex.

The lachrymal fluid is clear and watery and hypertonic in respect of plasma

<i>Constituents %</i>	
Water	- 98.2 gms.
Solids	- 1.8 "
Protein	- 0.67 "
Chloride	- 0.66 "
Glucose	- 0.65 "
Na	- 0.44 "
K	- 0.12 "

Lysozyme of tear secretion has a bacteriostatic effect. Tears flowing into the inner angle of the eye are aspirated into the lachrymal canaliculi and are collected in the lachrymal sac and pass through lachrymal duct into nasal cavity.

Contraction of the orbicularis helps in this. Paralysis of the muscle causes overflowing of the secretion. The lachrymal sac when affected by disease can be removed without any ill effects.

Mechanism of secretion: The secretory and vasodilator fibres to the gland arise in the pons and passing through the 7th cranial nerve these reach the sphenopalatine ganglion. Fresh fibres from this are conveyed to the gland through the maxillary division of the V nerve. Pilocarpine, muscarine and acetylcholine are excitants to the gland. Atropine abolishes secretion. The sympathetic fibres which originate in the upper thoracic cord,

are relayed in the superior cervical ganglion. These pass upwards in the carotid plexus to gain access to the gland. Vasoconstriction and diminished secretion are the effects of sympathetic stimulation.

MOVEMENTS OF THE EYE

Each eye performs several fast and precise movements that are closely associated with the movements of the other eye. Any movement of an eye involves at least two (extrinsic) muscles.

There are six extrinsic muscles for each eyeball. The four recti (superior, inferior, internal and external) arise from a fibrous ring (tendon of Zinn) attached to the margin of optic foramen. Their fibres travel forward, opening out so as to form a pyramid with four sides. The internal and external recti end as flat tendons and are inserted just behind corneal margin in a line parallel to it. The superior and inferior recti are inserted lateral to the mid plane of the eye behind the corneal margin, but the line of insertion is not parallel to it. The superior oblique arises from the orbital wall and passes forwards, upwards and medially. Its tendon passes through a fibrous ring (acting like a pulley) and goes backwards and downwards under the superior rectus and is inserted on the supero-posterior and external aspect of the eyeball. The inferior oblique arises from the inferior and medial angle of the orbit and passes outward under the eyeball getting insertion in its posterior and lateral aspect.

The 3rd or oculomotor nerve supplies all extrinsic muscles except the lateral rectus (supplied by the abducent or sixth nerve) and the superior oblique (by the fourth or trochlear nerve).

The movements of the eyeball: A denervated eye looks slightly outward. At rest, the eyes look forward, their axes being parallel. When fixation of the eye on an object occurs, eyeballs move so that the images are formed on corresponding points of both the retinae and kept in that position by rapid synchronous twitches of the muscles.

All movements of one eyeball are closely associated with the movements of the other one and this is made possible

by association fibres between the cranial nerve nuclei in pons and brainstem on either side of the midline. Also, connections exist between cortical centres and vestibular centres on one hand and the third nerve nuclei on the other. These cortical centres govern the associated movements of the eyes and head and conjugate movements of eyeballs.

A) The eyeballs can be turned in one direction or the other voluntarily in two ways :—

- 1) Conjugate movements occur when distant objects are looked at, one after another. The visual axes of the two eyes are kept parallel throughout the movement and later when the movement ceases.
- 2) Convergent movements are seen when a very near object is viewed – as in reading a book or in sewing. The medial recti of both eyes contract and cause the visual axes to meet at the object to be examined.

B) Reflex movements of the eyes are elicited in the following cases :

- 1) Fusion reflex – when the images of the same object are formed in the two eyes at different (non-corresponding) points of the retina, the positions of the eyeballs are corrected to shift the images on to corresponding points on both sides, so that cerebral fusion of the two images can result.
- 2) Fixation reflex – This results in both eyes being directed towards the same object when it comes into the visual field.
- 3) Postural reflexes – See labyrinthine and tonic neck reflexes acting on the eyes (postural mechanisms).

THE PHYSIOLOGY OF THE EYEBALL AND ITS APPENDAGES

The human eyeball (globe) is approximately spherical with the antero-posterior diameter 24mm and the vertical diameter 23.5mm. There are actually two spheres, one inside the other, the smaller one (formed of cornea) placed anterior to the larger one with part of it outside the latter. The anteriormost point on

the cornea and the posteriormost point of the larger sphere behind are known respectively as the anterior and the posterior poles. The straight line joining the two poles is the optical axis. An imaginary line running round the eyeball (circumference in a frontal plane), midway between the two poles, is the equator of the globe. The visual axis connects a point slightly medial to the anterior pole with the fovea centralis (lateral to the posterior pole) and it passes through the lens at a point just behind its centre. The tenon capsule is a fibrous covering for the eyeball and encloses it from the point of entry of the optic nerve (medial to the posterior pole) upto just behind the corneal margin where it blends with the sclera. The extrinsic muscles pierce it in front of the equator to gain insertion to the eyeball and check ligaments arise from the muscle sheaths to be attached to the orbital walls and these prevent excessive movements of the eyeball. Ciliary vessels and nerves also pierce the tenon capsule around the optic nerve. Areolar tissue fills the narrow space between the globe and the capsule and this serves as a cushion to protect the eye as it moves in the orbit.

THE EYEBALL

The conjunctiva: a delicate mucous membrane covers the exposed part of the eye (except the cornea) and it is reflected onto the inner surface of the eyelids. It is kept moist by the lachrymal secretion.

Tunics of the eyeball: The wall of the eyeball is composed of three concentric layers. (Fig. 63)

- I. an outer or fibrous tunic—sclera and cornea.
- II. a middle vascular tunic—choroid, ciliary body and iris.
- III. a nervous tunic—retina.

I. Sclera: It covers the posterior $\frac{5}{6}$ th of the eyeball and is hard, tough, fibrous and opaque. It is composed of white fibrous tissue and hence called the white of the eye. Where it joins the cornea, there is a groove. The junction is called the sclero-corneal junction. At the point of the entry of optic nerve, it is very thin and it is pierced by vessels and nerves and is

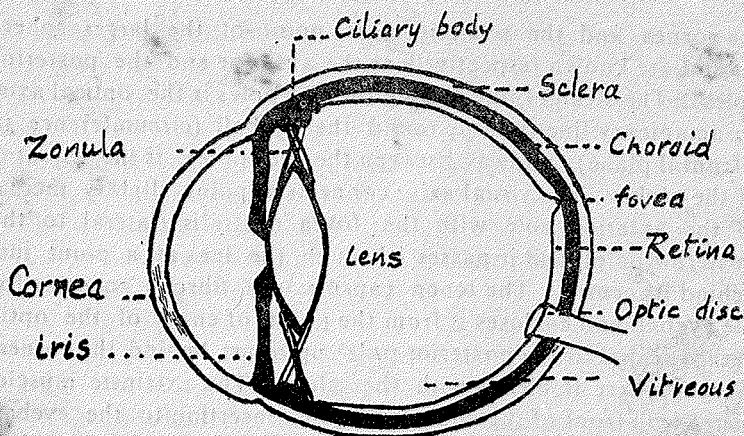


Fig. 63. The Eyeball

called the lamina cribrosa. (It is weak and forms a cup in glaucoma).

Cornea: It is convex anteriorly, being a part of a small sphere of radius about 7.7 mm and almost circular in shape and 0.5 to 1mm in thickness. It is transparent and consists of the following layers from without inwards.

1. Corneal epithelium—continuous with conjunctiva and formed of several layers of cells.
2. Anterior elastic lamina of Bowman.
3. Substantia propria—tough transparent membrane of flattened lamellae, composed of bundles of connective tissue fibres and continuous with the sclera.
4. Posterior elastic lamina of Descemet.
5. Endothelial layer.

The cornea is devoid of blood vessels (avascular), but it obtains its nourishment from lymph derived from vessels at its circumference which percolates through the intercellular spaces. It is also supplied around its circumference by plexuses of pain fibres, which enter cornea through the posterior elastic lamina and form plexuses in the substantia propria. From these plexuses, fibres proceed outwards through the anterior elastic lamina to

from a subepithelial plexus, from which again fibres go to the epithelial cells. They have a very low threshold for stimulation and ordinarily subserve only the pain sensation and no other.

The cornea is the most important of the optical media of the eye (having a refractive index of 1.37 and hence a power of 41-45D as a lens), since light rays in entering the eye have first to undergo refraction at the corneal surface.

The middle vascular tunic: It consists of, from behind forwards, choroid, ciliary body and iris.

II. Choroid is separated from retina by 1. structureless membrane of Bruch, 2. pigment layer of retina. It is composed of a rich capillary plexus and the numerous small arteries and veins leading to and away from it. It is dark brown in colour due to pigment cells present in it and it forms the middle layer over the posterior $\frac{5}{8}$ ths of the eyeball. It terminates anteriorly at the ora serrata of the retina.

Ciliary body: It is a circular ring of tissue extending forward from ora-serrata of retina to a short distance from the circumference of the lens. It is covered on its inner aspect by the pigmentary layer of the retina.

There are three parts in the ciliary body – orbicularis ciliaris, the ciliary processes and the ciliary muscle. The orbicularis immediately adjoins the choroid. It is a band of 4 mm width, present all round the eyeball. There are a number of parallel arranged ridges on its inner surface and known as ciliary processes, about 70 in number. They are triangular elevations on the inner aspect of the ciliary body, forming the corona ciliaris which encircles the equator of the lens at a distance to it and not touching it. The ciliary processes and muscle make up the bulk of the ciliary body. The ciliary muscle consists of outer meridional fibres and an inner circular set of fibres. The meridional fibres arise from the scleral spur and run back to be inserted into the ciliary processes. The circular fibres are few and form a network-like ring or band. The circular fibres of the ciliary muscle, together, constitute the Mueller's sphincter or

muscle. The inner fibres are attached to an elastic band at the angle of the iris. The outer fibres are connected to the elastic fibres continuous with the fibres of choroid.

The Iris: It is the most anterior part of the vascular tunic and is a thin contractile disc perforated a little to the nasal side of its centre, by the pupil whose margins rest on the anterior surface of the lens. The space bounded by the posterior surface of cornea and the anterior surface of the iris is called the anterior chamber and the space between the lens and the iris, the posterior chamber. Both the chambers communicate through the pupil and are filled with a clear watery fluid, the aqueous humour.

The periphery of the iris is attached to the anterior surface of the ciliary body and it is continuous through the pectinate ligament with the posterior elastic lamina of the cornea. The five layers of the iris from before backwards are:

1. Anterior epithelium of flattened cells.
2. Anterior limiting membrane.
3. Stroma – Loose connective tissue which transmits the vessels and nerves and contains branched cells which in dark eyes contain pigment granules.
4. Posterior limiting membrane.
5. Posterior epithelium.

The stroma contains the sphincter pupillae muscle of the iris about 1mm broad which, when contracted, causes constriction of the pupil.

The dilator pupillae muscle is seen in the fourth layer (posterior limiting membrane), the fibres of which converge towards the pupillary margin where they blend with the sphincter muscle. They arise from the ciliary body. When they contract they dilate or enlarge the pupil. The posterior epithelium has, two layers of deeply pigmented cells. It is the continuation of the Pars ciliaris retinae. Blood supply to iris is by circulus arteriosus minor at the pupil margin and circulus arteriosus major at the periphery, connected by arteries to the former. Blue or grey eyes owe their appearance to the transparency of

unpigmented stroma making visible the pigmented posterior epithelium. Pigment cells of stroma are responsible for the colour of the eye, in dark eyes. At birth, in babies of white races, pigment is absent in stroma and so the eyes are blue till a few weeks later. In babies of dark races, pigment is present in stromal cells even at birth and so the eyes are dark from the beginning.

Functions of the Iris:

1. It serves as an opaque screen and diaphragm to control the quantity of light reaching the retina.
2. It prevents light from passing through the periphery of lens and thus minimises chromatic and spherical aberration and thereby brings about a well defined retinal image.
3. When the pupil constricts, the depth of focus of the eye is increased.

The Pupil: In man, the pupil is circular. It is oval in the horse and the sheep and a vertical slit in the cat (daytime). Size of the pupil varies under different conditions. Contraction is known as myosis and dilatation as mydriasis. Pupil is larger in woman than in man. In children and the old, pupil is smaller.

In emotional states, pupil dilates. In sleep, pupil is constricted.

Innervation: The iris is supplied by sympathetic and the parasympathetic nerves. Sympathetics supply the dilator and the parasympathetics the constrictor of sphincter muscle. There are centres in the hypothalamus and the spinal cord and also in the cortex.

Sympathetic:—There is a centre in the posterior hypothalamus and a pupillodilator centre in the spinal cord in the intermediolateral column, extending from the last two cervical segments to the first four dorsal segments. Preganglionic fibres leave from the centre through the white rami communicantes and travel up the cervical sympathetic chain to the superior cervical

ganglion. Postganglionic fibres are conveyed in the peri-arterial plexus around the internal carotid artery to enter the fifth cranial nerve and finally traverse the long ciliary nerves and end on the muscle fibres of the iris. An injury to the superior cervical ganglion causes Horner's syndrome (miosis, ptosis and enophthalmus).

Parasympathetic : A constrictor centre exists in the anterior hypothalamus. Close to the third nerve nucleus is the Edinger Westphal nucleus from which fibres arise and run along with those of the third nerve and end in the ciliary ganglion. Postganglionic fibres which form twenty short ciliary nerves end in the sphincter muscle.

Drugs acting on iris :—

A. Mydriatics

Adrenaline
Ephedrine
Benzidrine

Sympathomimetic agents acting by stimulation of dilator muscle.

Atropine
Homatropine
Scopolamine

Parasympatholytic drugs paralysing the sphincter pupillae muscle.

B. Miotics

Choline derivatives
Pilocarpine
Muscarine
Eserine (phystigmine)

Parasympathomimetic substances exciting the sphincter pupillae muscle.

Ergotamine
Ergotoxine

Sympatholytic drugs causing relaxation of the dilator fibres.

Morphine which is a powerful miotic does not belong to any of the above categories.

THE LENS

The crystalline lens (about 20 D power at rest) is biconvex and its shape can be altered so as to focus the image of an object

clearly on the retina whether the object is placed at a distance or near the eye. The centre of its anterior surface is opposite the centre of the pupil.

Anatomy : The lens is a transparent and elastic structure having no blood vessels or nerves. It is suspended in the posterior chamber by the zonula or the suspensory ligament attached to the ciliary body and to the anterior and posterior surfaces of the lens. The posterior surface of the lens is more convex than the anterior one. The rounded edge of the lens is its equator. The lens is made of concentric layers of greatly elongated epithelial cells covered by a thin elastic permeable membrane. The central 'nucleus' is formed of older fibres. With age it loses water and hardens. It becomes less elastic and its optical properties change. The lens contains water, salts, protein and fat. In cataract formation, water increases at first and later decreases, when cataract is mature. Also, calcium content increases in this condition. Light rays are normally, partially absorbed by the lens. If infra red and U.V. rays are absorbed in a considerable proportion they can damage the lens, especially if it is exposed to them for prolonged periods. The proteins are responsible for the absorption of these rays. Lens respire by oxygen derived from aqueous humour.

Accommodation : The eye, at rest, is focussed for distant vision. When near objects have to be viewed, the eye undergoes changes, referred to as accommodation, collectively.

Purkinje-Sanson Images : (Fig.64) If a subject seated in a dark room has a lighted candle placed to one side of his head at 50cm. distance from the eye and is asked to look at a distant object, an observer looking at the subject's eye from the opposite side will see three images reflected by the subject's eye.

- 1) The brightest image is caused by reflection at the anterior surface of the cornea and it is erect and small.
- 2) The second image is also upright and much less bright but larger in size than the first. This image is due to reflection at the anterior surface of the lens.
- 3) The third image is the smallest and it is inverted and bright. This is due to reflection by the posterior surface of lens acting as a concave mirror.

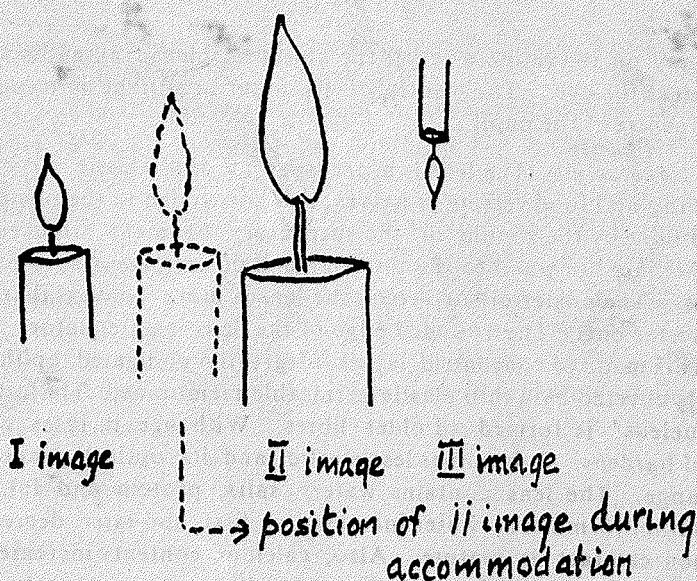


Fig. 64. Purkinje Sanson Images

If the subject, next looks at a near object in front of him, the first and the third images do not change in any respect but the second image becomes smaller than before and approaches the first one owing to an increase in the curvature of the anterior surface of the lens and the lens surface approaching the cornea and reducing the depth of the anterior chamber. These observations were first made by Helmholtz by the use of his phakoscope.

Changes in the lens during accommodation: If a near object is looked at, the curvature of the anterior surface increases in the central part (fig. 65) but diminishes in the peripheral parts. The posterior surface also becomes slightly more convex. The dioptric power of the lens, therefore, increases. Range of accommodation is measured in diopters and at birth is about 14D. It decreases with age, especially after 40 years, when reading or doing any work that requires near vision becomes difficult. This condition is known as Presbyopia.

Associated phenomena: The pupil is constricted for near vision. Marginal rays are eliminated and aberrations are corrected. The increase in the depth of focus also improves the

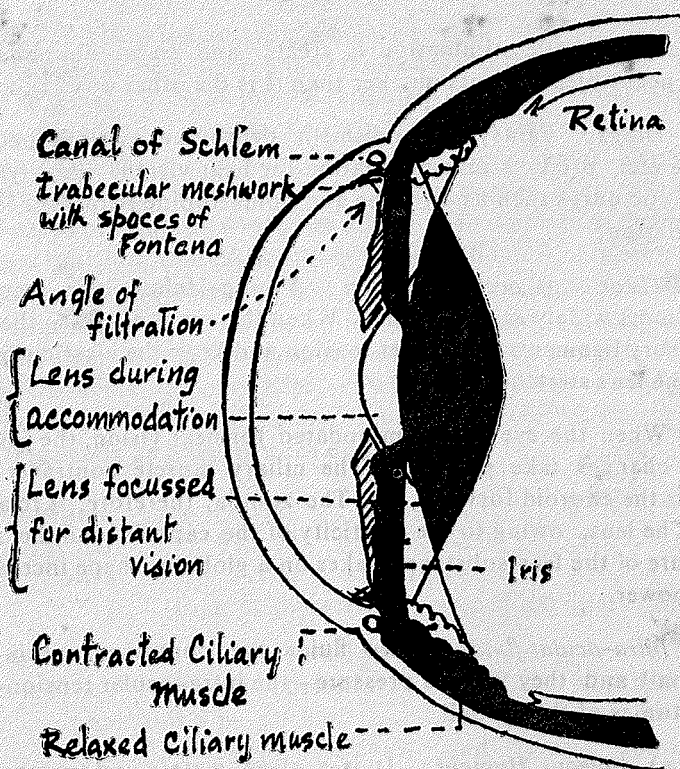


Fig. 65. Mechanism of Accommodation

definition of the image. The visual axes of the two eyes converge so that the images are formed on corresponding points of retina in the two eyes.

The changes in the shape of the lens are dependent on the action of ciliary muscle and the suspensory ligaments of the lens.

The contraction of the ciliary muscle brings about a relaxation of the suspensory ligaments (see below) and thereby an increase in the convexity of the lens. Stimulation of 3rd nerve and short ciliary nerves causes accommodation for seeing near objects. Stimulation of cervical sympathetic causes flattening of the lens and adjusting it for distant vision. The effect of the

parasympathetic stimulation is greater and so accommodation for near objects occurs quicker than it is the other way.

Drugs : Parasympathomimetic drugs like eserine, pilocarpine etc., produce accommodation for near vision. Parasympatholytic drugs such as atropine and homatropine paralyse accommodation.

Theories of accommodation : Young-Helmholtz's theory is the most widely accepted one. When the eye is at rest, the suspensory ligaments are under tension and keep the elastic capsule of the lens stretched.

When the eye is accommodated for near vision, the following changes take place—1. The ciliary muscle contracts and pulls the choroid forward, 2. The zonula, therefore, is relaxed, 3. The lens, owing to the elasticity of the capsule and the fluid nature of the lens substance, takes on a globular shape increasing its power.

Intra-ocular fluids : Two fluids are contained within the eyeball and they exert a pressure—the intra-ocular tension—on the tunics of the eyeball.

a) **Aqueous Humour :** It is a clear, watery and transparent fluid circulating in the anterior and posterior chambers of the eye. It serves as a nutrient for the lens and also is responsible for intraocular pressure. In man, the volume of aqueous humour is about 150 c.mm. In extreme myopia, it may be about 250 c.mm. It has much less protein than blood plasma. Other substances occur in more or less the same concentration. Glucose, amino acids, urea and chlorides are in less concentration. The refractive index of aqueous and vitreous humors is 1.33.

Formation is said to be by the process of dialysis and filtration and also by an active secretion. Fluid oozes out of the surface of ciliary body and posterior aspect of iris.

Circulation : Aqueous humour is evacuated by three routes.

a) The posterior route—through the zonula, the canal of Cloquet extending from the posterior surface of lens to the optic disc and the sheath of optic nerve.

- b) The crypts in the anterior surface of the iris also reabsorb the fluid to be delivered into the vessels of the iris.
- c) The canal of Schlemm, a circular venous channel which surrounds the cornea like a ring, at the angle formed by cornea and iris. It is separated from the anterior chamber by trabeculae which arise from the cornea and form the spaces of Fontana which open out towards anterior chamber but not into the canal of Schlemm. The iridocorneal angle is called the filtration angle. Some workers opine that there is a continuous absorption of the aqueous by the canal of Schlemm. Others hold that absorption occurs only when intra-ocular pressure rises, as when the eyelids close. The aqueous humour is renewed many times every day, even as frequently as once in three minutes.

Composition :	A. H.	V. H.	B. Serum
Water	99.692	99.682	93.323
Solids	1.086	1.108	9.536

(Figures represent grams per 100 mls. of fluid)

Vitreous humour : A colourless transparent jelly-like fluid fills the space between the posterior surface of the lens and the retina. It contains a network of thin fibres (which can be seen with an ocular microscope). Its density and freezing point are similar to those of aqueous humour. It has, however, a higher protein content, having a mucoprotein and vitrein which give it the consistency of a gel. It is denser nearer the retina than at the lens region.

Intra-ocular Pressure : (I.O.T)—This is measured, in animals, by putting a needle into the eye and measuring by a manometer or in humans, by pressing over with fingers or by a Schiotz tonometer. Normal pressure is 20-25 mm Hg, the range being 12-35 mm Hg. It diminishes from childhood to old age. It is higher in the morning than in the evening. A record of I. O. T. shows slight rhythmical variations with the systolic and diastolic changes in blood pressure and also corresponding to respiratory movements. The undermentioned factors influence I. O. T —

1. Pressure in the capillaries of the choroid.
2. Arterial blood pressure.

Effects of drugs on I. O. T. :—

1. Adrenaline diminishes it after a transient increase.
2. Eserine increases it.
3. Atropine has no effect in normal persons but increases in glaucomatous individuals.

I. O. T. is high in glaucoma and atropine should not be used in these cases. High intra-ocular pressure interferes with the eye and may even lead to blindness.

THE RETINA

The retina is a part of the central nervous system, as revealed by its embryology and histology. It consists of two concentric parts – an outer pigmentary layer and an inner nervous layer, the pars optica. The pigmentary layer prevents extraneous light from entering the eyeball. The pars optica is transparent in the living eye and is made of nervous and neuroglial elements. It lines the inside of the posterior part of the eyeball and ends anteriorly in a jagged edge – the ora serrata. The origin of the optic nerve

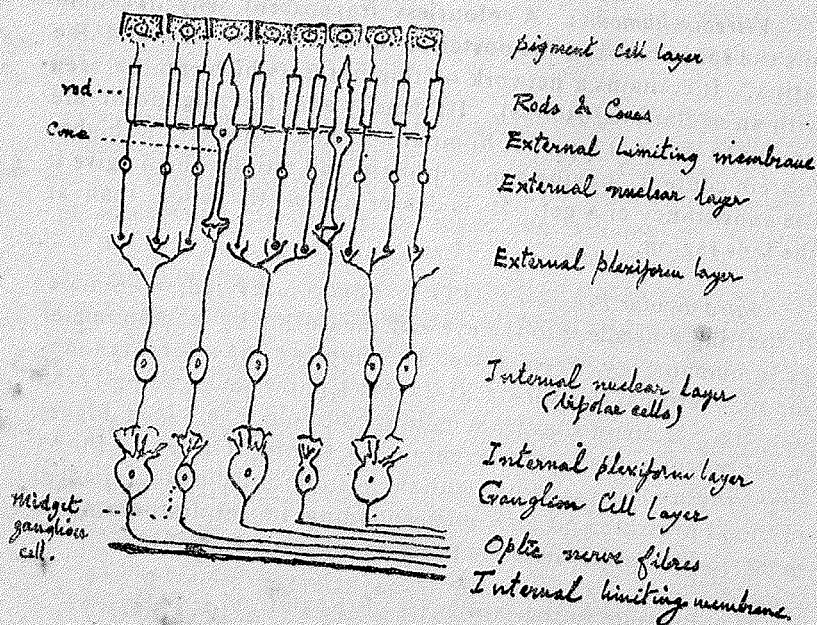


Fig. 66. The Retinal Layers

trunk is seen as the optic disc – a pale oval or circular disc, 1.5 mm in diameter, located 3 mm medial to the posterior pole of the eyeball and about 1 mm above the horizontal plane passing through the posterior pole. A yellowish area (3 sq. mm) called the macula lutea lies lateral to the posterior pole, 3.5 mm from the optic disc. In the centre of this area is a depression, the fovea centralis, functionally the most important part of the retina for daylight vision. The pars optica is formed by 9 layers (excluding the pigmentary layer outer to it). From without inwards, they are:

1. Layer of rods and cones.
2. External limiting membrane formed of neuroglial elements
3. Outer nuclear layer
4. Outer plexiform layer
5. Inner nuclear layer
6. Inner plexiform layer
7. Ganglion cell layer
8. Layer of optic nerve fibres
9. Internal limiting membrane

The photoreceptors are the rods and cones which occur in the outermost layer of the pars optica. They have a common embryonic origin and each of these exhibits three intracellular parts :—

1. an external photosensitive part – the so called distal segment.
2. a middle part containing a nucleus.
3. an internal process which synapses with the dendrons of the bipolar cells whose cell bodies lie in the inner nuclear layer.

There are about 7 million cones in the human retina. The fovea centralis has only cones in it. The cones in this part (central retina) are extremely slender and longer than those in the rest of the retina where they are shorter and thicker compared to rods. In the extrafoveal or peripheral retina, the cones diminish in number and the rods increase numerically in the

anterior direction, each cone being surrounded by several rods. The entire retina has about 120 million rods in it. The external process of the rod contains the photosensitive pigment, rhodopsin. There are no cones in the retinae of the rats and night flying birds and no rods in those of the day flying birds.

The nerve cell elements in the retina and the visual pathway form a chain of three links--the photoreceptors which send impulses to the bipolar association cells in the middle layers of the retina. In the fovea centralis, it has been seen that the outer 4 layers (see fig. 66) only are present, the elements of the inner layers having been pushed away from the fovea so that their cellular and fibre elements are crowded at the edge of the fovea. This arrangement is to avoid absorption of light energy by the inner layers as the rays pass through the retina to strike the receptors. Further, since visual acuity is the highest in foveal vision, this histological arrangement makes possible such high activity.

The foveal cones discharge impulses, each into one bipolar cell (midget bipolar cell) whereas in the other parts of the retina, several receptors communicate with one bipolar cell. Thus, in the fovea there is, at least functionally if not structurally, a one to one relationship between the cones and the bipolar cells. In other retinal sites, there is a many to one relationship between the receptors and bipolar cells. The peculiar cellular arrangement of the fovea in relation to the bipolar cells is held to be responsible for the high visual acuity of foveal vision. The bipolar cells in their turn, communicate with the ganglion cells and even here, the one to one arrangement as between the foveal receptors (cones) and the midget bipolar cells, holds good for the midget bipolar cells in respect of the ganglion (midget) cells. In other words, the cones of the fovea have an exclusive or preferential central pathway through the midget bipolar and midget ganglion cells. All the other receptors are made to converge on to bipolar cells which are less in number and the latter have to converge in their turn on to ganglion cells which are about a million in number.

THE VISUAL PATHWAY

The visual pathway (fig. 67) is said to be made of 3 neurones, the receptors not being counted as nerve cells. The axons of the

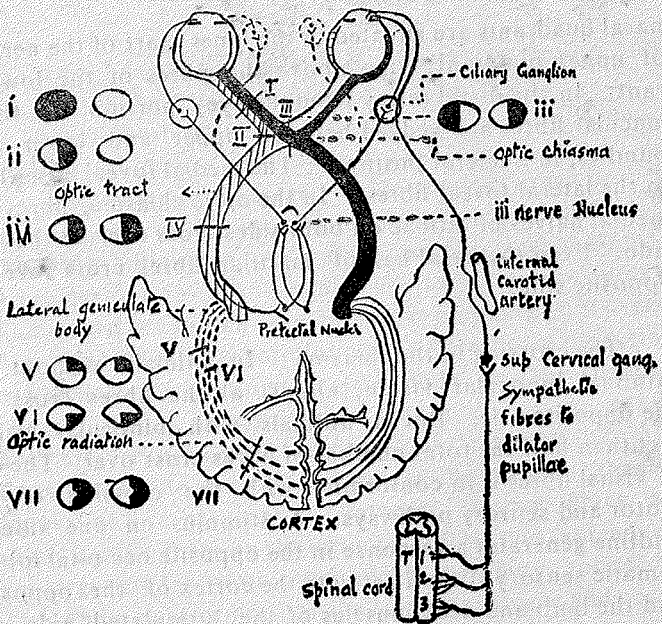


Fig. 67. Nerve Pathways Concerned with Vision
 (After Duke-Elder, S., *Parson's Diseases of the Eye* (15th ed, 1970),
 J & A Churchill Ltd., Ltd. p. 353)

ganglion cells situated all over the retina converge towards the optic disc in the manner of the spokes of a wheel. But those arising from ganglion cells in the lateral parts of retina do not directly approach the optic disc, but arch around the macula so as not to lie in the path of light rays travelling towards the fovea. All the fibres are gathered together to form the optic disc whose free surface lies almost flush with that of the retina itself. In the optic nerve itself, the various fibres do not mix indiscriminately. Their retinal origins are reflected in the regular spatial arrangement of fibres in the optic nerve and further on in the central reaches of the optic pathways. The macular fibres retain their identity throughout the visual pathway. They are separated from the rest of the retinal fibres. All along the visual pathway, a rather systematic arrangement of fibres from different retinal areas, is present. In the optic nerve, fibres from the upper and lower temporal quadrants are found in the upper lateral and lower lateral portion of the nerve, respectively. Fibres from

nasal quadrants are situated in the inner part of the nerve, fibres of upper quadrant lying above the fibres of the lower quadrant. In the distal (away from the eye) portion of the nerve, macular fibres are wedged between upper and lower temporal bundles, in a lateral position. The medial foveal fibres lie medial to the lateral foveal fibres. In the optic chiasma, fibres from the medial halves of retinae on both sides cross over to the opposite side. Even the nasal half of macular fibres cross over to the opposite side.

The crossing in the chiasma: In animals without or with minimal binocular vision, almost all the fibres cross over to the opposite side. But in animals with binocular vision, not less than half the total number of fibres cross over. The crossing of visual fibres is in conformity with the crossing of somatic motor and sensory pathways. A stimulus on one side of the midline generates a response in the opposite occipital lobe. Also, somatic sensory stimuli activate the cortex of the opposite side and the limb and neck muscles of the stimulated side will be made to execute movements by the motor area of the opposite side of the cortex, which is excited by the visual and somatic stimuli. The crossing of all these pathways avoids confusion in the nervous mechanisms. The fibres of the optic nerve which form the optic tract behind the chiasma, terminate in the lateral geniculate body in its dorsal part. The lateral geniculate body is composed of 6 laminae of grey matter with intervening white matter between every two adjacent layers. The laminae are numbered 1 to 6 from external surface inwards. The crossed fibres of the optic tract end in cells of 1st, 4th and 6th layers, the uncrossed fibres in 2nd, 3rd and 5th layers. Each fibre of the optic nerve, on its way to the lateral geniculate body, divides into three branches, each passing to a different lamina. This is in apparent support of Young-Helmholtz's Trichromatic theory. Thus, the three laminae might possibly be concerned with the three fundamental colour sensations—red, green and blue. But there is no physiological evidence for this, however. In higher animals, the lateral geniculate body projects entirely to the cortex. Removal of striate area causes rapid atrophy of all neurones in the lateral geniculate body on the same side.

In the lateral geniculate body also, a discrete point to point representation of the retina is present. The upper parts of peripheral retina, both nasal and temporal, project to the medial parts of the lateral geniculate body and the lower parts to the lateral part, the macula to a large wedge-shaped area between the superior aspects of the lateral and medial parts of the lateral geniculate body. Binocular and monocular vision seem to have separate representations in the geniculate body. In the monkey, monocular vision occupies a very small rim on the ventral aspect. There seems to be a rigid separation of the fibres from the retinae of the two sides in the lateral geniculate body, so that fusion of the two retinal images, necessary for binocular vision, cannot take place here. Fusion seems to occur only in cortex. The 3rd order fibres from the lateral geniculate body pass through posterior part of internal capsule between sensory fibres and auditory radiations, forming the optic peduncle and spread out to form a large flat fan (optic radiation) sweeping round the lateral wall and posterior horn of the lateral ventricle and bending into the temporal lobe forming the Meyer's loop, which contains fibres relaying those from the lower quadrants of the two retinae. A temporal lobe tumour can affect these fibres to cause contralateral superior quadrantic hemianopia. The upper retinal fibres are spared. The fibres of the upper and lower retinal quadrants separate, as the radiation turns backward to the calcarine cortex. The fibres relaying those arising from the retinal portions above the horizontal meridian enter the cortex above the calcarine fissure and those corresponding to the lower retinal portions below the fissure. The bundles from various parts of the retinae are segregated from each other even here. The geniculo-cortical fibres end in the 5th layer of the cortex. The point to point projection is a functional one in that there is a preferential path from one cone, say, to one cortical cell. A spreading of the impulse is possible, but in effect, the projection of the retina remains more or less punctate.

The representation of the retina in the cortex is shown in the figure (Fig. 61). The macula has a relatively much larger cortical area which lies more posteriorly than the one for the peripheral retina which extends more anteriorly on either side of the calcarine fissure. Macular vision is spared in unilateral

lesions of the optic pathway. The underlying anatomical basis is not clear. It is also possible, among several explanations, that a substitute macula may develop in the retina on account of eccentric fixation of the eyeball, as a compensatory adjustment, on the affected side.

The area on the two sides of the calcarine fissure on the medial surface and to a small extent on the lateral surface also of the occipital pole which receives the optic radiations, is the primary visual area or the striate area (Area 17 of Brodmann). Adjacent to this are the area 18 (parastriate area) and area 19 (peristriate area) which are visual association areas (fig.61). These do not have direct connections with the visual pathway with which they have links only through the primary visual area. The two visual association areas are thought to have the functions described below.

Area 18 — It is held to be responsible for bringing about functional association between the primary visual areas in the two hemispheres. It may be involved in the establishment of conditioned reflexes utilising visual stimuli. The visual recognition of familiar objects (animate and inanimate but not for written matter) is a function assigned to this area. Visual agnosia or failure to identify previously known objects, is a sign of a lesion in this area.

Area 19 — The ability to recall the physical aspects of objects seen before, is a faculty that is subserved by the area 19. This is also one of the cortical suppressor areas. Motor effects elicited from the area 4 can be suppressed by simultaneous excitation of the area 19 which, however, does not exert its effect through the mediation of the caudate nucleus, unlike the other suppressor areas (2s, 4s, 5s and others). Lesions in the areas 18 and 19 cause disturbance in spatial orientation and stereoscopic vision.

DUPLICITY THEORY OF RETINAL FUNCTION

Max Schultz proposed the duplicity theory of retinal function which implies that the two retinal receptors, rods and cones

subserve different though complementary functions. The rods function at low levels of illumination (dim light vision; night vision; scotopic vision) and help in the mere detection of objects in the visual field. The making out of fine details in objects seen, as well as the appreciation of colours, is taken to be the function of the cones and hence these receptors are responsible for colour vision (daylight vision or photopic or bright light vision). There is quite an impressive accumulation of experimental evidence to support the concept of duplicity in the retina. A subject is made to remain in a dark room and his threshold

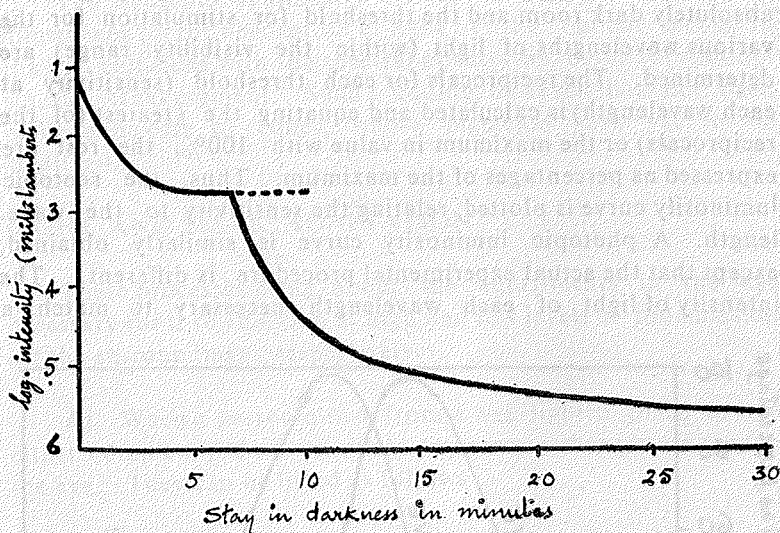


Fig. 68. The Dark adaptation Curve

(After Best, C. H. and N. B. Taylor, *Physiological Basis of Medical Practise*, 8th ed., (1966), The Williams & Wilkins Company, Baltimore, p. 297).

for light stimulus is determined at various intervals from the time he entered darkness. If a graph is plotted (fig. 68) relating the fall in threshold (reciprocal of sensitivity) with the passage of time in darkness (dark adaptation), it shows initially, a rapid fall (in threshold) continued by a slow fall and this is interrupted by a break which is followed by another (lower curve) phase of rapid fall in threshold which is continued by a slower phase and then levelling off. The first part of the curve indicates the rise in

sensitivity of the cones, the later part represents the rise of the sensitivity of the rods. The Purkinje phenomenon is also taken to be the outcome of the presence of two receptors, each with a different function. In bright light, yellow coloured objects appear brightest of all, whereas in fading light, green appears to be the brightest colour. Purkinje phenomenon has an experimental basis in the shape of luminosity curves which can be obtained as follows :

For the scotopic luminosity curve, the subject sits in an absolutely dark room and the threshold for stimulation for the various wavelengths of light (within the visibility range) are determined. The reciprocals for each threshold (sensitivity at each wavelength) is calculated and equating the greatest (of the reciprocals) or the maximum in value with 100%, the rest are expressed as percentages of the maximum. Thus, the scotopic luminosity curve is plotted, relating the sensitivity to the wavelength. A photopic luminosity curve is similarly obtained, except that the actual experimental procedure is different. The intensity of light of each wavelength necessary to match a

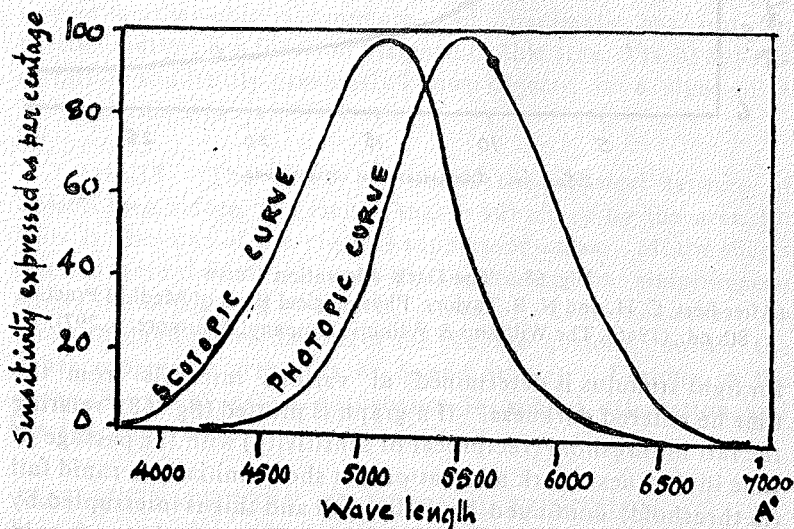


Fig. 69. Luminosity Curves
(After Best, C. H. & N. B. Taylor, *Physiological Basis of Medical Practice*, 8th ed., (1966), The Williams & Wilkins Company, Baltimore, p.300.

standard illuminated patch is determined and its reciprocal derived. Expressing all the reciprocals as percentages of the maximum value observed, the photopic luminosity curve is plotted on the same X-axis as for the other curve.

The scotopic luminosity curve has a maximum at wavelength 510 $m\mu$ (green), while the photopic curve has the maximum at 560 $m\mu$ (yellow). These maxima, one for each curve, provide an objective proof for the Purkinje phenomenon.

The scotopic luminosity curve, if modified by making allowances for the absorption of light by the optical media in the eye, coincides with the spectral absorption curve for rhodopsin, the visual pigment. Such a finding, however, has not been made in the case of cones, whose pigments have yet to be identified.

LIGHT AND DARK ADAPTATION

These processes bring about the adjustments in the eye necessary for it to function at high and low levels of illumination (of the surroundings), respectively.

A) When a person moves from a well-lighted place to one either completely dark or dimly lit, certain changes are seen in the eye. They can be listed as follows :

- 1) In the beginning, nothing is visible (if one enters an area of complete darkness) or objects appear very hazy. With the passage of time in the new surroundings, the visual sensitivity (of the retina) increases (see Duplicity Theory) to a maximum in about 30 minutes. Objects are better seen, not only with their outline made out but also with a few of the more gross details. But colour appreciation will be absent and visual acuity will be low at low intensities of external lighting. The retinal sensitivity maximum also shifts from yellow to green (Purkinje shift).
- 2) The pupil dilates immediately following the fall in the level of illumination, but the dilatation is not maintained. With the rise in sensitivity of the retina, the pupil reassumes a

smaller size. Size of the pupil seems to bear a definite relationship to the intensity of illumination after adaptation has taken place, though in the beginning there is a swing too far in the direction of dilatation, since the retina has not adapted itself sufficiently to the low levels of illumination.

- 3) Regeneration of visual purple, bleached under conditions of bright light, is promoted in darkness.
- 4) It may be mentioned that if the retinal tissue has an acid reaction in bright light, it is changed to one of alkalinity in darkness.
- 5) No structural changes, as far as is known, take place in the retinal receptors, unlike in sub-mammalian forms.

B) When a subject comes out of darkness (or dimly lit surroundings) into an area of bright light, the changes mentioned above are reversed. Light adaptation takes place more rapidly than dark adaptation.

1. Initially, there is a sense of dazzling which may be painful and gives rise to defensive responses like covering the eyes with the hands. Retinal sensitivity to light diminishes sufficiently in a short time to establish clear vision. Full colour appreciation and high visual acuity are restored in bright light. Reverse of Purkinje shift occurs.
2. The pupil constricts in the first few moments, but later enlarges somewhat, keeping pace with the fall in the retinal sensitivity. The pupil assumes a size intermediate between that in darkness and the constriction in the beginning and appropriate to the intensity of light to which the eye has adapted.
3. Visual purple gets bleached.
4. The retinal tissue exhibits a change in reaction, from alkalinity to acidity.

PUPILLARY CONSTRICTION AND DILATATION

Pupillary constriction occurs under the following circumstances which mostly (except in cases mentioned below) bring about excitation of the third nerve nucleus.

- a) light reflex resulting from light entering the eye and exciting the receptors (see light adaptation also).
- b) as an associated change in the near or accommodation reflex.
- c) during sleep.
- d) due to the action of miotics like morphine and eserine which directly act on the constrictor muscle fibres.
- e) in anaesthesia during the stage of induction.
- f) in lesions of the spinal cord affecting the cervical segments which give off the preganglionic sympathetic pupillo-dilator nerves and Horner's syndrome arising out of injuries to the superior cervical sympathetic ganglion.

Pupillo dilatation is seen in the following conditions :

- a) excitation of the sympathetic nervous system (as in fright and anger)
- b) due to injuries of the third nerve.
- c) on cessation of a light stimulus, as happens when the eyes are shielded or on entering a dark room (see dark adaptation).
- d) when the eye is focussed for distant objects after viewing near objects.
- e) reflex dilatation resulting from the stimulation of any sensory nerve in the body.
- f) in the fourth stage of anaesthesia, with commencing bulbar paralysis and in coma.
- g) glaucoma — high intra-ocular tension.
- h) there is a curious reflex whereby pinching or any other form of stimulation of the skin of the neck brings about the dilatation of the pupil (cilio-spinal reflex).

CHANGES IN THE RETINA ON EXPOSURE TO LIGHT

These have been conventionally described under four headings 1. Structural 2. Physical 3. Chemical and 4. Physiological.

1. The undermentioned structural changes seem to be reflex effects which have been observed in the retinae of lower animals, especially reptiles. Though these have not been described explicitly in the human retina, it is possible that similar

changes occur and are most probably mediated by the descending fibres in the visual pathway which may be concerned in some form of control over the behaviour of the retinal receptors. From recent work, it is being realised more and more that such efferent control by the cortex obtains in the case of receptors of other categories (eg. hair cells in the cochlea) too. The pigment outside the retina proper moves inwards so as to lie between the cones which themselves undergo some degree of shortening. Also, chromatin granules in the ganglion cells have been observed to disappear.

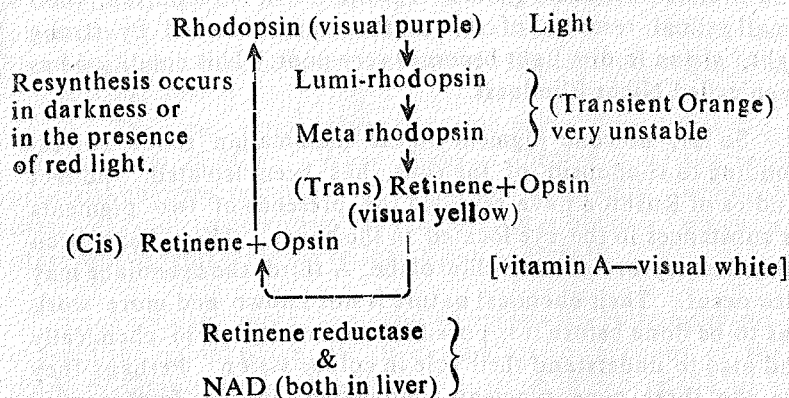
2. The physical change is manifested in the form of the electroretinogram (see elsewhere for details).

3. Chemical changes are of two kinds. The retina which is a piece of nervous tissue depends for its energy, mainly on glycolysis. Consequently, when the retina is excited by the incidence of light on it, glucose breakdown is hastened leading on to the formation of pyruvic or lactic acids which tend to alter the reaction of the retinal tissue to the acid side of neutrality. The more important of the chemical effects is what is known popularly as the bleaching of the visual purple.

Rhodopsin: Kuhne, in 1879, isolated this carotenoid pigment from the frog's retina which, histologically at least, appears to have mostly, if not completely, rods. This pigment is of a rosepink colour and is situated in the outer segments of the rods but not in the cones. It is a conjugated protein with a prosthetic group — retinene, a derivative of vitamin A. This pigment is broken down by the action of light, both when it is found intracellularly and also in solutions (in vitro). This action, known as the bleaching action, causes the disappearance of the colour of the pigment. While all wavelengths in the visible spectrum are efficient in bleaching rhodopsin, yet green rays seem to be most effective. When the minimal intensities of the different wavelengths required to bleach the visual purple (in vitro) are determined and their reciprocals are related to the wavelengths, the spectral absorption curve of rhodopsin is obtained. This coincides perfectly with the dark adaptation curve (see elsewhere), when the necessary allowances for absorption of light by the ocular media in the eye are made. In darkness, visual purple is regenerated and for this the

rods should be in contact with the cells of the pigmentary layer which appears to have some essential role in the regeneration. The breakdown (bleaching) and the regeneration of rhodopsin is a cyclical process going on constantly in the eye. George Wald was one of the pioneer visual biochemists who elucidated the series of changes undergone by the pigment during the bleaching process. He received the Nobel prize for his work in this field.

WALD'S CYCLE



The arrows pointing downwards indicate changes occurring in the presence of light.

Retinene is chemically an aldehyde derivative of vitamin A which is an alcohol which corresponds to Lythgoe's Visual White.

In the changes depicted schematically above, it is during the conversion of Lumirhodopsin to metarhodopsin that nerve impulses are thought to be generated in the optic nerve. The terms used by Lythgoe and others are shown within brackets opposite the chemical terms representing the different stages. This correlation is at best an approximate one.

The retinene which splits off from opsin (left behind in the retina) is carried away in the blood stream to the liver, where, by the action of an enzyme, retinene reductase and the co-enzyme, nicotinamide adenine dinucleotide - NAD (DPN is the older term), it suffers an isomeric change from the trans-form to the

cis-form and the latter is brought back to the retina where resynthesis into rhodopsin occurs. In states of vitamin A deficiency, the body reserves of vitamin A are at a very low level. When the trans retinene is transported to the liver, it undergoes conversion to the cis-form in which it is released into the blood stream again. But, since the blood level of vitamin A is very low, the level of cis-retinene (released) in the blood will also be low and sufficient cis-retinene cannot reach the retina to bring about resynthesis of the pigment. Hence, vitamin A deficient subjects find it difficult to see objects in dim light. If, in addition, their small retinal reserves of the pigment are bleached by strong light, vision in dim light becomes very poor. This condition has been called Night Blindness.

So far, no cone pigment in the mammalian retina corresponding to rhodopsin of the rods, has been isolated. Indirect studies of Rushton have revealed the presence of two pigments or substances in the eye located in the cones. These have been named as erythrolabe and chlorolabe. A third, the cyanolabe may also occur. Their chemical nature is not known and more work has to be done before it is possible to identify them chemically and also to understand their role in colour vision. Perhaps they are the three cone pigments implicated in the Trichromatic theory. In the retina of the chicken, which is purely of the cone type, Wald isolated another carotenoid pigment, iodopsin, which has an absorption maximum around 575 millimicrons near the yellow part of the spectrum. The significance of this finding in the function of cones is yet to be realised.

4. *Physiological effect of stimulation of retina by light:* The exact effect depends on whether the cones or rods or both are stimulated. It suffices in this context, to merely say that the sensation of light is a physiological consequence of the incidence of light in the eye.

THE ELECTRICAL ACTIVITY OF THE RETINA

Four types of electrical activity can be seen in the retina:—

1. The steady corneo-retinal potential (30-60 mv) with the cornea positive in respect of the retina. The underlying basis is not clear, but this may arise in the membrane of Bruch.

2. Fluctuating potentials caused by throwing light into the eye—the electroretinogram.

3. By the use of micro-electrodes placed in contact with the inner retinal surface, the activity of individual ganglion cells can be recorded. Some of these (on-elements) respond to illumination, but become inactive in darkness. Others are activated only when light thrown into the eye is switched off (off-elements). Some others become active when light is switched on and again when light is switched off (on and off elements). When micro-electrodes are made to enter the retina so as to come into contact with the inner nuclear layer, spikes can be recorded on throwing light, but the exact identity of the cells of origin for this is uncertain.

4. The action potentials in the optic nerve fibre. *The electroretinogram (ERG)*: When light is thrown into the eye, potential changes occur in the retina and a graphic record of these has come to be known as the electroretinogram, which in other words represents the retinal action currents.

Even though, more than hundred years ago, Holmgren discovered the retinal potentials, it was mainly on account of the work of Granit that it has become possible to understand to a great extent, how the electroretinogram changes arise. Recent work of Brown and his colleagues has thrown more light on this matter.

In the simplest set up for recording the electroretinogram, a wick electrode is placed on the cornea and this serves as a recording electrode and an indifferent electrode is placed in the mouth, the two electrodes being connected to a sensitive galvanometer. In animals, a decerebrate preparation gives very satisfactory results, especially with the pupil dilated by drugs. The indifferent electrode is placed on the brain stem above the level of section.

The following features or potential changes are seen in an ERG — The ERG manifests itself after a short latent period from the onset of illumination. The form of record varies with the state of adaptation of the eye and with the wavelength of the incident light. The set up for recording is so arranged that

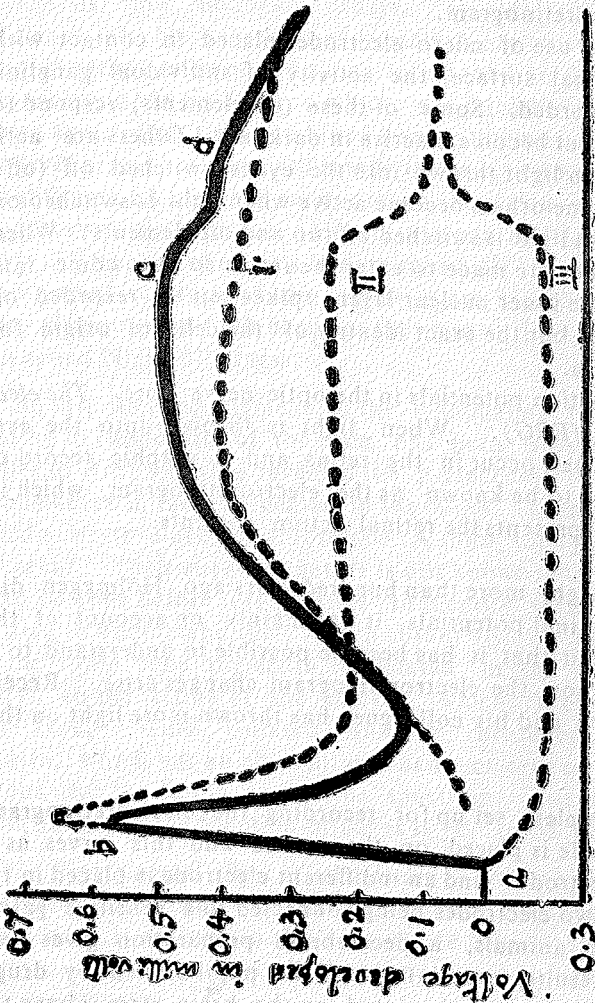


Fig. 70. The Electoretinogram

(After Best, C. H. & N. B. Taylor, *Physiological Basis of Medical Practice*, 6th ed., Williams & Wilkins Company, Baltimore, p. 1131)

corneal positivity is seen as an upward deflection. In general, there are 4 waves seen in the ERG — an initial negative 'a' wave followed by a large positive one, the 'b' wave, which is succeeded by a slowly rising 'c' wave and when light is switched off another positive deflection, the 'd' wave (the off element).

Granit considered the ERG as resulting from the superposition (algebraic summation) of three fundamental components—PI, PII, and PIII. PI is a slowly developing positive component which disappears when intense light is used or after light adaptation. PII is more rapid in its time course and gives rise to the 'b' wave. PII as well as PI may arise in the bipolar cells. PIII is in the downward direction and gives rise to the 'a' wave initially. But when light is switched off, the upward swing of PIII is reflected as the 'd' wave. Based on the presence or absence of the negative 'a' wave, Granit concluded that there are two kinds of retinae in animals. Those in which the ERG shows a prominent 'a' wave are said to have I-type retina (I-inhibitory). These retinae have a predominance of cones and have been compared to a slate which has to be wiped clean everytime before writing on it—before a new image is formed on the retina leading to a new sensory experience. The pigeon and the light adapted frog have this kind of retina. When the ERG does not show the negative 'a' wave (P III), such a retina is considered to be of the 'E' type (E – excitatory). The cat, the rat and the guinea pig possess such a retina in which the rods are the predominant receptors. To sum up, PIII indicates inhibitory activity, PII being associated with optic nerve activity and the 'b' wave is a measure of the sensory response of the retina as a whole, to light. Granit's nomenclature of the three 'P' components is based on the ease with which they can be abolished during ether anaesthesia, as its depth is increased. PI is the earliest to disappear, followed by PII and PIII, as the anaesthesia is deepened.

The investigations of Brown and his colleagues have shed some more light on the cellular origins of the different components of the ERG. The 'a' wave is best recorded with an electrode in the region of the membrane of Bruch, and it seems to arise in the outer segments of the receptors—the rods and the cones. Consequently, PIII should originate in the receptors. The 'b' wave may owe its occurrence to the activity in the outer plexiform layer whose activity itself is derived from the excitation of the bipolar cell layer and the ganglion cell. The 'c' wave is taken to be the result of the excitation of the cells in the pigmentary layer, though it also is best recorded from the membrane of Bruch.

Clinical importance of the ERG : While the ECG and the EEG are of considerable diagnostic and prognostic significance, the same cannot be said of the ERG which is of limited clinical value. When the receptor layers in the retina are damaged, the ERG cannot be recorded.

In the rare, hereditary condition of retinitis pigmentosa, the ERG disappears even before there is a serious loss of vision. As one author puts it, the ERG itself needs to be explained rather than it being explanatory, in relation to the disorders of vision.

Physiologically, a dark adaptation curve is obtained when the intensities of various wavelengths in the visible spectrum, required to give rise to a 'b' wave of constant height in the ERG, are plotted against the respective wavelengths. This curve is identical with the dark adaptation curve obtained by using threshold intensities for various wavelengths during dark adaptation. This implies that the threshold for 'b' wave is related to that for scotopic vision.

VISUAL FIELD AND EFFECTS OF LESIONS IN VISUAL PATHWAY

When each eye is directed forwards without shifting the gaze to one side or the other, it is able to simultaneously see all objects as fall within a certain area, which is the visual field. Its limits or boundary can be represented in a single plane graphically, on a paper in which the different planes in space are represented by radial lines diverging away from a central point of fixation at which the eye is directed. Concentric circles are drawn round the point of fixation, each denoting the visual angle subtended by two diametrically opposite points on each of the circles. The visual field for each eye can be plotted separately by the use of a perimeter. The visual fields for colour vision also can be obtained by the use of the same instrument, but with coloured discs or lights. The field for a normal eye as constructed on the perimeter chart, has a roughly oval shape (fig. 71). In the vertical plane, superiorly, the field extends upto the circle corresponding to 50 degrees of visual angle. Downwards, it

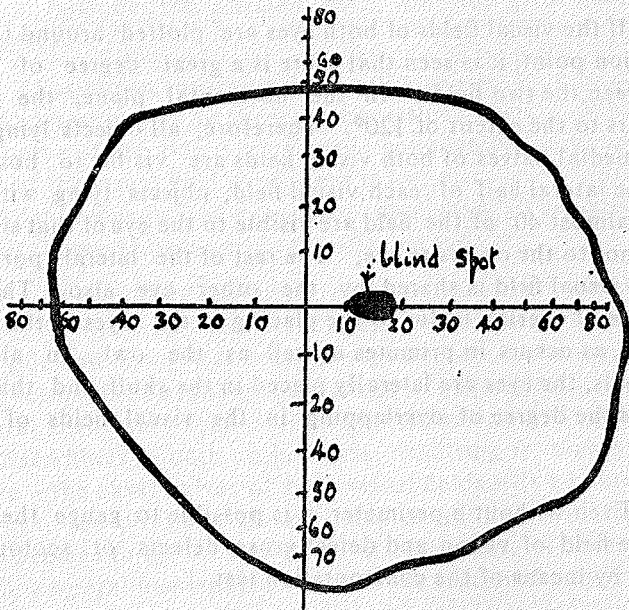


Fig. 71. Visual Field of Right Eye

extends to the 70° circle. Hence, the entire vertical diameter of the field is 120°. The smaller extent in the upwards direction as compared with that in the downwards direction is due to the presence of the supra-orbital ridges of the frontal bone. Medially the field extends to the 60° circle only, the limit being imposed by the nose. Laterally, the 90° circle is the boundary for the visual field. Thus, the horizontal range in the visual field is about 150°. There is a small oval area lying between the 10 and 20 degrees circles, lateral to the point of fixation and in the horizontal plane, which is the blind spot corresponding to the optic disc in the retina where no receptors occur (physiological scotoma). Objects lying within this small area will not be visible to the eye tested, provided the other eye is closed. Normally, no one is aware of the blind spots in the two eyes, when both eyes are open. This is because, the blind spot in the visual field of one eye is not the blind spot for the other. In other words, in binocular vision when an object falls within the blind spot of one eye, it throws an image on a functionally active part of the retina in the opposite eye.

If the visual fields of both eyes are plotted around the same fixation point, it is seen that there is a great degree of overlap between the two fields. In the horizontal plane, the overlap occurs to the extent of 120° . Therefore, all objects lying within the medial halves of both visual fields are visible to both eyes. In the lateral half of each visual field, objects lying within the lateralmost 40° of the field are visible to the eye of that side only, but not to the opposite eye. The rest of the lateral portion of each visual field is shared by the other eye also. This high degree of overlap is due to the placing of the eyes in the frontal plane, as occurs in primates as well as the owl. In all other animals, the eyes are laterally placed in the skull and this minimises the degree of overlapping in the visual fields of the two eyes.

Even without a perimeter, it is possible to gauge the extent of the field of vision and detect gross defects or scotomata, if any, by means of the confrontation test.

LESIONS IN THE VISUAL PATHWAY AND THEIR EFFECTS

The plotting of visual fields of subjects who have lesions in various situations, either in the retina or in the visual pathway itself, provides accurate clues to the location of such lesions and so the procedure can serve as a useful diagnostic aid. The effects of such lesions are named by the actual defects in the visual fields and the terminology is not based on the anatomical sites of such lesions. The term, scotoma or blind spot (scotomata-plural) refers to a defect in the visual field. The various possible lesions in the retina and the visual pathway itself are now referred to along with their effects, in anatomical sequence—

1. A small localised lesion of the retina in one eye gives rise to a scotoma in the visual field of that eye only. It is to be remembered that a lesion in the lateral half of the retina is reflected as a defect in the medial half of the visual field and vice versa. Likewise, a retinal defect above the horizontal meridian gives rise to a scotoma in the lower half of the visual field and vice versa. If a greater portion of the retina is damaged, light,

when it falls on the affected part, will not give rise to the light reflex.

2. Lesions in the optic nerve will give rise to effects more or less corresponding to those of the retina itself. When the optic nerve of one side is sectioned completely, not only the whole of the visual field of that eye is lost, but in addition the direct light reflex in that eye is also abolished. The consensual reflex is, however, retained in the affected eye.

3. At the site of the optic chiasma, an aneurysm of one internal carotid artery will press upon the uncrossed fibres of the same side and hence will bring about a defect in the medial half of the retinal field of the ipsilateral eye. Theoretically speaking, bilateral aneurysm of the internal carotid artery will involve the uncrossed fibres of both optic nerves, resulting in binasal hemianopia – the nasal halves of both visual fields will be absent. A tumour of the pituitary gland, being a midline structure, will cause damage to the crossed fibres of both sides. The result will be a bitemporal hemianopia – loss of the temporal halves of both visual fields.

4. When the optic tract is involved in a lesion, homonymous hemianopia is the consequence. In a lesion of the right optic tract, the result will be a left homonymous hemianopia and vice versa. In the former case, the left halves of both visual fields are lost. It has already been pointed out that when light falls on a diseased portion of the retina, the light reflex cannot be elicited. It is however, difficult to stimulate one part exclusively. All the same, a clinical condition, known as Wernicke's hemianopic pupil, results from a lesion of the optic tract. That is to say that when light is thrown on the affected halves of the two retinae, the light reflex fails. However, it is very difficult to demonstrate this feature. A lesion in the lateral geniculate body which is a circumscribed mass will give rise to the same effects as in the case of the optic tract. But the light reflex will be left intact.

5. With temporal lobe lesions affecting the Meyer's loop, a superior quadrantic hemianopia in the halves of the two retinae will be the effect. When the Meyer's loop on the right side is affected, the result is left superior homonymous quadrantic hemianopia.

6. Since the fibres of the optic radiations diverge away from each other, a localised cortical lesion will affect only a minority of the geniculo - calcarine fibres. Thus, only small scotomata will be seen and these are present in the halves of the opposite side in the visual fields on both eyes.

Argyll-Robertson pupil : In some cases of cerebrospinal syphilis, the pupil exhibits the near reflex but not the light reflex. The condition may be unilateral or less commonly bilateral. The affected pupil is miotic and does not respond to light or even mydriatics. Much discussion has arisen with regard to the actual location of the lesion, in this condition. It is most likely that the light reflex fibres are affected at a site lying between the point of divergence of the reflex fibres from the main visual pathway and the third nerve nucleus. In the present state of knowledge, it is not possible to be more precise than this.

ACUITY OF VISION AND REFRACTORY ERRORS

The eyes, as optical instruments, are capable of a high degree of resolution. In common terms, the eyes enable us to see and appreciate minute details in the objects seen. The smallest visible detail expressed in terms of its visual angle gives a measure of the visual acuity. Visual angle is the angle formed at the optical centre of the eye by two rays of light emerging from the extremities of an object. Based on determinations of visual acuity in a very large population of normal subjects (without any discernible refractory errors), the normal standard for visual acuity in human subjects is taken as 1' (one minute) of angle. There are however, some subjects with greater visual acuity (less than 1' of visual angle) than this somewhat arbitrary standard of 1'. That is to say that in general, all objects which subtend less than 1' of angle at the eye cannot be made out by the normal eye. Minimum visual angle is also referred to as minimum separable (by distance or angle). In other words, visual acuity is measured in terms of the smallest distance or angle between two point sources of light necessary for their recognition as separate points. With shorter intervening distances, the two points will be seen as one only.

Visual acuity can also be expressed in terms of minimum visible and Vernier acuity. Even a point source of light placed at a great distance from the eye, if it is sufficiently intense can be visible. The stars in the night sky are the best examples for this. The visual angle subtended by them is in geometrical terms much below the minimum separable. But they are seen because of their very intense emission of light. The ability to perceive breaks in a straight line or minute misalignments in a Vernier calipers or screw gauge, is referred to as the Vernier acuity which is of a much higher order than the minimum separable. Vernier acuity as low as 4" or 5" has been observed.

Visual acuity, as measured in terms of the minimum separable, depends on many factors. Those pertaining to the retina are—the site of retina tested, diameter of retinal receptors, the state of adaptation of the eye. Those concerning the stimulus are—the intensity of illumination of the test object, the wavelength used for illumination. The visual acuity is the highest when foveal vision is used and it falls steeply when the peripheral retina is employed for testing. Visual acuity is low in dark adaptation on account of only the rods being active. In conditions of bright light, foveal or cone vision gives rise to high visual acuity. In the fovea where a one to one relationship obtains between the cones on the one hand and the bipolar cells and the ganglion cells on the other, the diameter of the cone ($2.5-4\mu$) imposes a limit on the visual acuity. At least one unstimulated cone should lie between two stimulated cones (by two point sources of light) in order that they may be seen separately. The maximum visual acuity observed in foveal vision (slightly less than 1" of visual angle) is in conformity with the view that cone diameter is a factor involved. But Vernier acuity cannot be explained on this basis. It looks as if very small differences between one cone and the next one in the amounts of light energy (flux) falling on each can be detected by the eye and it is attempted to explain Vernier acuity on this basis. It is a common experience that when minute objects are examined visually, it is found necessary to increase the illumination of the objects. For example, reading and sewing need stronger light than other tasks. In addition to the intensity of the illumination of the test object being viewed by the eye, the contrast provided by the

background also has some importance in determining the visual acuity.

On theoretical grounds and in conformity with the trichromatic theory of colour vision, the visual acuity when using monochromatic light, for example, of one of the three primary colours, should be less than that for white light. But strangely enough, there is no significant difference as regards visual acuity between that for white light and that for any of the monochromatic lights. This fact was a stumbling block for the acceptance of the trichromatic theory. Hartridge rescued the trichromatic theory by advancing what he called as the cluster hypothesis. According to this author, the three types of cones are not distributed uniformly or even randomly over the retina or even in the fovea. Each type of cone is present in clusters or groups of its kind only. Thus, for example the 'red' cones are present in compact groups. In each group, the other two types of cones are not present. When monochromatic light is used, that part of the fovea which has the appropriate clusters of cones in relation to the incident wavelength, is directed towards the light rays. This hypothesis gives a convincing explanation for the absence of any disparity as regards visual acuity, between monochromatic lights and white light.

The dimensions of the test objects used for testing visual acuity as well as its shape also, seem to matter in visual acuity determinations.

Tests for visual acuity: The most common test employed makes use of the Snellen's test types. On a large white card there are several rows of letters printed, each row expected to be clearly seen by an emmetropic eye at a particular distance noted against it. In each row, all the letters are of the same size. The greatest dimension of each letter (height) subtends a visual angle of $5'$, while the edges of each of the lines forming the letter forms an angle of $1'$ at the eye, when looked at from the distance appropriate to it. Each row has smaller letters than the one above. Alternatively the Landolt 'C' can be employed.

At best, test types are the means of a subjective way of testing. The ophthalmologist can have recourse to retinoscopy, by means of which, not only the presence of refractory errors is

established, but also the actual quantitative information regarding the defect, can be obtained. Details concerning retinoscopy are found in treatises on ophthalmology.

REFRACTORY ERRORS

The human eye is heir to several defects. Some of these are seen in all eyes since they are common to all optical instruments, man made or living. As for the other kinds of refractory errors, they result from disproportionate development of the eyeball.

Spherical aberration and chromatic aberration are inherent in all optical instruments. The human eye is no exception. Spherical aberration is minimised in the eye by pupillary constriction which cuts off all the rays of light passing through the peripheral parts of the lens. But when pupillary constriction is of a high degree, diffraction of light rays may result. Nevertheless, spherical aberration and diffraction are not consciously experienced by the eye. Chromatic aberration is minimised or abolished by as yet ill understood mechanisms. Pupillary constriction reduces chromatic aberration by blocking rays entering the eye through the lense periphery. It is never a cause of eye strain.

Stiles-Crawford effect: It was observed that when a pencil of rays enters the eye through the pupil, the rays passing through the central part of the lens do not undergo any modification with regard to any of the three qualities or parameters of light (hue, saturation and brightness). But those which enter the eye near the pupillary margin suffer certain modifications like loss of brightness, change of hue and loss of saturation as well as a greater deviation. Also, visual acuity is greater with regard to the central rays which strike the retinal receptors in the end on position. The peripheral rays meet the receptors at an angle to their axes. The importance of pupillary constriction in minimising the aberrations natural to the eye, follows from the facts of this phenomenon.

The actual refractory errors of clinical importance are myopia, hypermetropia, astigmatism and presbyopia.

Emmetropia: This condition obtains in the normal eye. Parallel rays of light (all distant objects are, for practical purposes, considered to emit parallel rays of light) are accurately brought to focus on the retina by the action of the refractory media of the eye. (fig. 72)

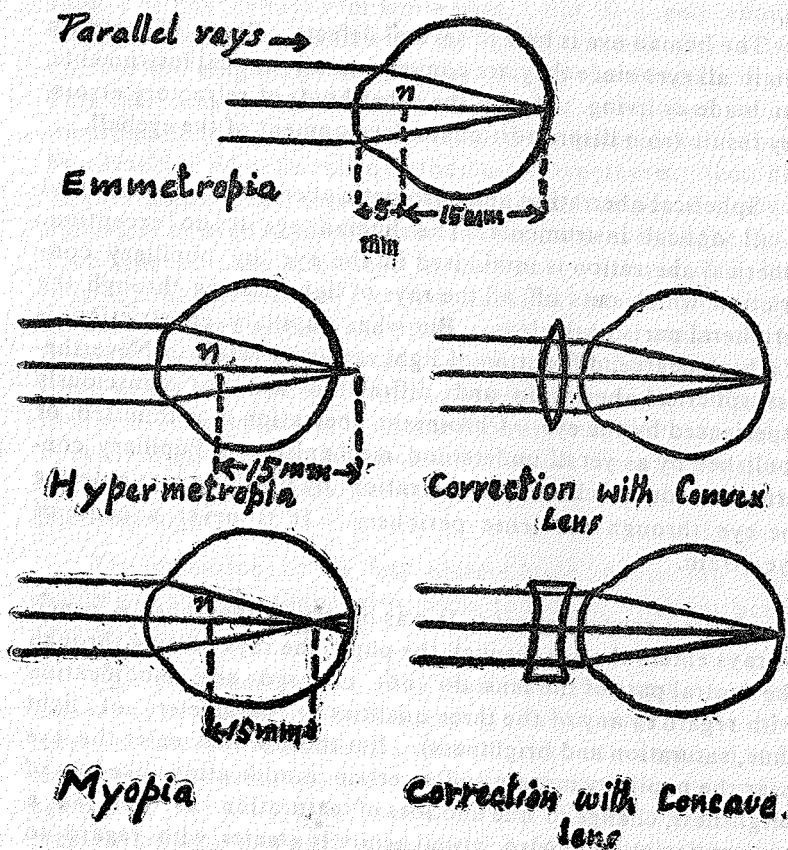


Fig. 72. Common Refractory Errors

Myopia is the state in which parallel rays are brought to focus by the refractory media of the eye at a point which lies in the vitreous itself and not on the retina. An undue lengthening of the eyeball in the anteroposterior direction during growth is the underlying cause. In other words, the lens system of the eye

(cornea, aqueous and lens) is too powerful or strong for the eye. Myopia is usually detected towards the end of the second decade of life when the disproportion between the length of the eyeball and its lens system becomes evident. Less commonly however, myopia may manifest itself at a very early age in childhood. This condition may increase in severity as growth takes place. The correction for myopia is by means of spherical, diverging (concave, negative) lenses of suitable power so as to bring parallel rays into focus on the retina itself. In the case of near vision, since the eye need not accommodate to the same degree as an emmetrope or in a hypermetrope (see below), the ciliary muscle is not exercised to the same degree as in the latter two conditions. Hence it is somewhat weak in action and less well developed.

Hypermetropia is the condition of the eyeball at birth in all subjects. As age advances, hypermetropia normally disappears yielding place to emmetropia. If, however, the growth of the eyeball is excessive, myopia results. In some subjects, however, the eyeball does not grow sufficiently so that it remains hypermetropic even in adulthood. The lens system is not powerful enough for the eyeball. In this condition, parallel rays are made to converge behind the retina. So, in order to bring about correct focussing on the retina, spherical, converging (convex, positive) lenses are prescribed. Since the eye has to accommodate even for distant vision, not to speak of near vision, the ciliary muscle is always in action, and consequently it is very well developed in hypermetropes. Hypermetropes have necessarily to wear glasses constantly. Otherwise, severe headache arising out of tonic ciliary contraction and also contraction of extraocular muscles will be caused. In fact, hypermetropes seek medical attention for headache as such and hypermetropia is diagnosed after the examination of the eye.

In normal eyes, the refractory power of the ocular media is uniformly the same for light rays lying in all planes in space. Sometimes the refractory power of the eye is different in different planes. For example, if light rays lying in horizontal plane are focussed on the retina accurately, those in other planes may either meet in front of the retina or

behind the retina. Astigmatism is the condition caused by non-uniformity of the refractory power in the different planes. The correction is by cylindrical lenses, either of the convex or of the concave shape with its axis correctly positioned to equalise the refraction in the different meridians of the eye. Cylindrical lenses, theoretically, are parts of cylinders, just as spherical lenses form parts of spheres. There is a slight degree of astigmatism even in the normal or emmetropic eye and this is referred to as physiological astigmatism which is of such a minor degree that it does not need correction by lenses.

In connection with accommodation it was mentioned that in old age, the range and amplitude of accommodation diminishes, the near point (at 10 cms from the eye normally) recedes from the eye. This is due to the hardening or sclerosis of the lens fibres making the lens material more or less solid in consistency and lose its inherent ability to assume a globular shape when the tension on the capsule is released by ciliary muscle contraction. The increase in the lens power of the eye necessary for accommodation, cannot be derived from the lens itself and hence converging lenses will have to be used. Presbyopia usually makes itself felt in the fifth decade of life in previously emmetropic individuals. In the case of myopes, presbyopia will be late in onset since the two conditions require opposite kinds of lenses for correction. There is a compensation of myopia by presbyopia. So, reading may be possible without glasses. The term 'second sight' is used in connection with the neutralisation of myopia by presbyopia. Even though both hypermetropia and presbyopia require correction by converging lenses, it is not justifiable on any grounds to consider presbyopia as hypermetropia of old age. The underlying causes are entirely different. In hypermetropia, it is disproportion between the size of the eyeball and its refractory power while in presbyopia it is the inability of the lens to change its shape in order to bring about an increase in its dioptric power.

In conclusion, it must be mentioned that the diminution in the range and amplitude of accommodation starts from childhood. But, presbyopia of a degree requiring correction by lenses is manifested only in the 5th decade of life.

BINOCULAR VISION AND STEREOSCOPIC VISION

Binocular vision: It has already been mentioned that the visual fields of the two eyes overlap each other over a span of 120° in the horizontal meridian, leaving only two crescentic areas, one on either side (temporal crescents) at the extreme lateral ends of the visual fields. Objects lying within the region of each temporal crescent are visible to the eye on that side only and thus, only monocular vision is possible in this area. But in the large area of overlap, all objects throw their images on corresponding points in the two retinæ. The two images are fused by the nervous action in the visual pathway. It is the fact that each object throws images in the two eyes so that they fall on corresponding points in the two eyes, which is responsible for fusion of the two images and hence for binocular vision. If the two eyes do not perform conjugate movements for an object to be fixated, fusion cannot occur as the images in the two eyes will be formed on non-corresponding points. Diplopia may result if the disparity between the two images is sufficiently great. This is what happens in squint or strabismus, as results from paralysis or even paresis of one or more of the extrinsic eye muscles. With small degrees of incoordination among the extra-ocular muscles, diplopia may be avoided by consciously trying to compensate for the incoordination. But with large degrees of strabismus due to serious injury or paralysis of one or more of the muscles, diplopia is inescapable. If this is not corrected by surgical treatment at a very early age, the image in the eye whose movements are at fault, will be suppressed and in course of time this eye will become functionless even though structurally it may not show any changes. It is necessary to stress that squint has to be corrected at a very early age and as soon as it is detected. Surgical intervention at a late date serves no purpose as one eye would have already become irrevocably functionless. The ability to fuse two complementary images is tested by means of the amblyoscope. In the absence of squint, the subject can easily bring about fusion of the two images formed by two complementary test objects – clock face and hands of the clock; a bird and an empty cage; a horse and its rider. In the presence of incoordination, fusion is not possible.

In passing, it is useful to mention that the retinal images of objects in the visual field are real, inverted and of a smaller size than the objects. But we are not aware of the image inversion. The mental correction of the inverted image takes place in early infancy and hence we are never aware of images being inverted in the eye.

Stereoscopic vision: The eyes enable us not only to appreciate the dimensions of objects in one plane but also the depth or the third dimension and this faculty is known as stereoscopic vision. Whenever an object is viewed with the two eyes simultaneously, even if the images in the two eyes are more or less on corresponding points, they are not strictly identical. The image in each eye represents the view of the object from that eye. Thus, each eye has its own view of the object. It is the difference between the two images that gives a clue to the sensorium (cortex) that the object is a solid one having three dimensions and not like a picture in one plane. There are subsidiary clues which also aid in stereoscopic vision. To mention some:—perspective, due to which parallel lines running away from the eyes seem to meet at a distance; a cube or an oblong object seems to taper off at its farther end; the effect of light and shade on the surfaces of solid objects or in the case of a sphere; the apparent changes in the colour of objects as exemplified by distant hills appearing blue while nearer ones have their natural colour; nearer objects hide farther objects even though the former may be much smaller than the latter; during a movement of the observer, parallax also helps—with nearer objects moving in a direction opposite to that of the observer, while farther objects seem to move in the same direction as the observer. It goes without saying that for stereoscopic vision, both eyes have to be used. Seeing with only one eye will give rise to an impression of flatness. But owing to long training in the perception of objects, stereoscopic vision may not be lost when only one eye is functioning because the various clues mentioned above can still aid in the perception of depth.

COLOUR VISION AND COLOUR BLINDNESS

The visible spectrum extends from about 760 millimicrons in the red, to about 400 m μ in the blue. The aphakic eye is

sensitive to the adjacent region of ultraviolet also, in response to which sensation of violet is caused. The infra-red region can excite the eye if sufficiently intense, when it causes the sensation of deep red. The physical characteristics of rays of coloured or monochromatic light (within the visibility range of the spectrum) are wavelengths, expressed in angstrom units and intensity — the energy transmitted. Corresponding to these are the respective subjective attributes—hue—the actual colour perceived and brightness, which however, is not entirely dependent on the intensity. The state of adaptation (see Duplicity Theory) and contrast are some of the factors involved in determining the brightness of a hue. Saturation is a third quality of coloured light. This depends on the admixture of the colour of a particular wavelength with white light. A hue is fully saturated if it is not contaminated with white which, when present, makes the hue unsaturated.

From the luminosity curves, it can be seen that under conditions of bright light, the retina is maximally sensitive to yellow, and to green, in dim light. This shift in sensitivity is known as the Purkinje shift. The rods contain rhodopsin, a carotenoid pigment, which is responsible for dim light vision. The exact nature of the pigments, if at all responsible for colour vision, is open to conjecture. However, Rushton has 'detected' two pigments in the cones from their behaviour. These are not chemically identified.

- 1) Erythrolabe, which is a red sensitive substance.
- 2) Chlorolabe, a green sensitive pigment

A third pigment, the cyanolabe, seems to exist, as revealed by later studies.

The normal human eye can distinguish about 160 different colours in the visible spectrum, in some regions of which a difference of as little as $3\text{ m}\mu$ in wavelength gives rise to a different hue experience. Cones are present exclusively by themselves in the so called rod-free area of the foveal centre — about 400μ in diameter. Beyond this region towards the periphery, the cones diminish in number, whereas rods increase. Though

originally, only the fovea was thought to be concerned in colour vision, it has now been amply demonstrated that peripheral retina also can give rise to colour appreciation. The fields of vision for the different colours are smaller than for white, though concentric with it. Thus, blue has the largest area, red coming next, the area for green being the smallest. The area for yellow is intermediate in extent, between those for red and blue.

Colour matching experiments: Thomas Young, more than a century ago, and Wright, very recently, showed that with a suitable mixture of three properly chosen primary colours—viz—red, green and blue, it is possible to obtain a match with any hue in the visible spectrum. For white, equal quantities of the primary colours should be mixed. These results formed the basis for the classical Trichromatic Theory of Colour Vision, originated by Thomas Young and later elaborated by Helmholtz and others.

The choice of the primaries is wide, though the primaries have to lie, one in the region of red, one in green and the third among the shortest wavelengths of the visible spectrum—i. e. blue. Also each of the primary colours should not result from a mixture of the other two.

It is seen that when a spectral colour is matched with a mixture of the three primary colours chosen for this purpose, the latter appears to be somewhat less saturated. For a perfect match, the hue matched with, has to be desaturated with white. Wright, however, has found three primaries, which are called fundamental primaries, whose mixture will give perfect matches (not unsaturated) with any spectral colour. These are a blue of $460\text{ m}\mu$, a green of $530\text{ m}\mu$ and a red of $760\text{ m}\mu$.

Complementary colours: These are pairs of colours whose mixture in equal proportions, gives rise to white. Thus, red and green, blue and yellow are two pairs of complementary colours. The existence of complementary colours can be easily inferred from the colour mixture experiments. For example, red and green and blue give white. Red and green will give yellow. So

it follows that blue and yellow will give white and are hence complementary.

COLOUR VISION THEORIES

Thomas Young propounded the well-known Trichromatic Theory of Colour Vision. Helmholtz, a little later, put this theory on firm foundation. The bed-rock of this theory is the fact that any spectral colour, as also white, can be matched by a suitable mixture of three, but not more or less number of colours (lights of different wavelengths), which are called the Primary colours. It was postulated that there are three types of cones, each being maximally, though not exclusively, sensitive to a certain part of the spectrum. The different hue experiences result from simultaneous excitation of the three types of cones, though to different degrees. Stimulation of all the three types of cones to the same degree, results in the sensation of white. Stimulation to an equal degree of the two types of cones which are sensitive to red and green parts, without exciting the third type of cone at all, will give rise to an experience of yellow. Thus, each hue is perceived by concomitant stimulation of the three types of cones, each to a different degree.

Facts in support of the Trichromatic Theory :

- 1) Colour matching experiments already referred to.
- 2) If one eye is stimulated with one wavelength and the other with light of a complementary colour, the sensation of white results. If red light is thrown into one eye and green into the other simultaneously, sensation of yellow results. This binocular fusion of colours is strong supportive evidence.
- 3) Colour defects like dichromatic and monochromatic vision can be very easily explained on the basis of Young-Helmholtz theory.
- 4) "Simultaneous and successive contrasts" can also be explained by this theory.

Hering's theory of opposite colour pair: Three photosensitive pigments are thought to occur in the retina. Each pigment is broken down by a stimulus of one colour, but resynthesized

by a stimulus of the opposite or the complementary colour. Thus, we have three pairs of opposite colours, namely :

- | | | |
|-----------|---|-------|
| 1. White | — | black |
| 2. Red | — | green |
| 3. Yellow | — | blue. |

The implication of this theory that both, the breakdown of a pigment by a stimulus and its resynthesis by one of the opposite colour, can give rise to stimulation of the same optic nerve fibre, is completely at variance with the concept of the specificity of the receptors and the physico-chemical nature of nerve action potential whose shape and size cannot be altered by a change in the quality of the stimulus. This is a very serious objection. Even though this theory was originally called a Tetrachromatic theory (Red-green, blue-yellow), it can be easily seen that this also is a kind of Trichromatic theory.

Hartridge's polychromatic theory was based on a number of conclusions drawn from many experiments of several investigators. It was an attempt to bring together many discordant facts. The colour matching experiments in which mixtures of only three primaries have been used to match any spectral colour, militate against Hartridge's concept. Sir C. V. Raman expressed his views on colour vision wherein he invoked the aid of certain pigments like Xanthophyll, the cytochrome enzymes (which are present in all cells). These are taken to act as visual pigments. In view of the presence of these in all cells, it is not at all possible or even reasonable to assign a visual function to them. He also, in contradiction of his own postulations regarding these pigments, assumes the existence of a multiplicity of receptors, in utter disregard of facts concerning visual acuity and much more so of those pertaining to colour matching experiments. It is unfortunate that, though on purely physical grounds his conclusions appeared valid to him, yet he has ignored all the fundamental investigations in the physiology of vision and of receptors in general and also the role of carotenoid pigments in vision. Raman's views are not at all acceptable.

The Young-Helmholtz Trichromatic theory is the only working hypothesis available at present. There are however, certain objections to this.

- 1) White and yellow do not appear as blended or compound sensations.
- 2) Peripheral colour vision is not explained by this, as well as sensation of grey.
- 3) The field of vision for yellow is much larger than for red or green. If yellow were to result from a red and green mixture, the field of vision for yellow should be smaller in area than for red or green. It should at least have the same extent as that of the smaller of the two—green.
- 4) Certain anomalous colour defects are not explained by this hypothesis.
- 5) Absence of three histologically differentiated types of cone in the retina is a notable objection, but not insurmountable, for, the differentiation may depend on the difference in pigments present which may be molecular and sub-microscopic.
- 6) The visual acuity for different colours is the same as for white. This fact apparently contradicts the Y-H theory, but recently Hartridge removed this objection by his cluster hypothesis.

Recent evidence in favour of Young-Helmholtz's theory:

From his studies on retinal units, Granit has found that though several types of modulators (each sensitive to a narrow part of the spectrum) exist in the retina, they could all be brought under three broad groups, each of which functions maximally in the region of one of the primary colours.

Le Gross Clark has demonstrated lamination of the lateral geniculate body as well as the three-fold division of each fibre in the optic tract. (See Visual Pathway)

The necessity for using three primary colours for effective matches with spectral hues, the inadequacy of only two primaries for this purpose and the superfluity of more than three primaries constitute the irrefutable foundation for the trichromatic concept of colour vision.

COLOUR BLINDNESS

The terminology for naming the different varieties of colour blindness is based on the trichromatic theory of colour vision. The three major categories of colour blindness are :

- 1) Anomalous trichromatic vision – a) protanomaly b) deuteranomaly c) tritanomaly.
- 2) Dichromatic vision – a) protanopia b) deuteranopia c) tritanopia.
- 3) Cone monochromatism.

In the first category, a subject needs a greater proportion of a particular primary colour in admixture with the other two primaries, to match with white. The protanomalous subject requires more of red, the deuteranomalous subject more of green and the tritanomalous person more of blue. A normal subject needs all the three primaries in equal proportion. It is implied that, of the three types of cones, one is not functioning at optimum level and hence for colour matching, the primary colour corresponding to the defective receptor is required in a somewhat greater proportion than in the case of normal subjects.

In dichromatic vision, only two of the three cones are functioning. Thus, in protanopia, the red sensitive cone is either absent or inactive. Among others, John Dalton, the famous English Chemist, was a protanope and he gave a classical description of his defect and was responsible for the recognition of colour blindness as a clinical entity. Similarly, in deuteranopia and tritanopia, green sensitive and blue sensitive cones are respectively affected. These subjects try to match all the spectral colours by means of only the two primaries to which they are responsive. The normal person needs all the three primaries. It follows that the colour matches made by dichromatic subjects will be entirely different from those of normal people.

In cone monochromatism, there is only one functional type of cone which is sensitive to the whole range of the visible spectrum, and the various colours appear as shades of grey, just as

in a black and white photograph. Visual acuity, however, is normal in these people. Very rarely, in some individuals, the retina may be cone free, giving rise to rod monochromatism. Their visual acuity is very poor and in addition they suffer from intense photophobia. This makes day light vision almost impossible for them. It is needless to say that colour vision is absent in this type also.

Tests for colour blindness : While it is not difficult to separate normal subjects from colour defectives by means of one or two simple tests to exactly pinpoint the actual type of colour blindness, it needs certain refined tests like the use of an anomaloscope and also spectroscopy which will not be described in this account.

a) *Holmgren's colour wool test :* A number of bits of wool of various colours are kept in a container. The observer picks out a bit of one particular colour and the subject is required to pick out all the pieces that match with the selected one. While the normal subject has no difficulty, colour defectives will pick out not only pieces of the same colour as the chosen one, but also those which give rise to confusion for the subject, who takes them to be of the same hue as the test piece. One drawback with this procedure is that the pieces of wool tend to become dirty with repeated usage. Also, these colours fade with the passage of time. So difficulties may arise even for normal subjects in correctly choosing the pieces.

b) *Ishihara's pseudo-isochromatic charts :* This test is also known as the hidden digits test. The tool used is a book of plates made up of digits formed of coloured spots set in a background which itself is made up of dots of colours, causing confusion with those forming the digits. The subject is asked to name or identify the digit or letter in the chart. While to a normal eye, a particular digit or letter stands out clearly, the colour defective person sees another digit or letter, which is not at all visible to the normal eye. As a routine, this has only a qualitative value. Precise diagnosis of the colour defect needs other procedures in addition.

c) *The Edridge-Greene colour perception Lantern :* This device helps in testing colour vision in the red-green part of the spectrum. This lantern consists of several circular metal discs,

all pivoted (in the vertical plane one behind the other) on a common stem. Each disc carries a number of small circular transparent pieces of glass, each of a different shade of red or green and simulating light signals as viewed under various atmospheric and weather conditions like rain, dust, storm, fog etc. Each disc can be rotated so as to bring any one piece of glass opposite an electric bulb in the interior of the instrument. The subject identifies and calls out the colour of the signal specifying that it is bright or dull and so on. This test has a restricted scope since it is used to detect only red-green confusion. But it is a practical means for eliminating colour defectives while recruiting candidates to the air force, the police and the railway services.

Visual contrast: When one sees a blue spot on a yellow background (blue and yellow being complementary colours since their mixture in equal proportions, gives white), the effect of either of the colours, blue or yellow, is heightened and each colour appears brighter than if it seen separately. This effect of one colour on its complementary colour when they are seen in juxtaposition, is called simultaneous contrast or spatial induction. Such an effect occurs even when an object of one colour is seen first and an object of the complementary colour is seen immediately thereafter. The second object appears brighter and more saturated than it would if the first object had not been seen. This phenomenon is known as successive contrast or temporal induction. Simultaneous contrast is a device used by painters as a technique to improve the appearance of pictures and make their different areas look brighter and prominent.

After-images: The persistence of a visual impression under certain conditions is known as an after-image. After-images are perceived after the visual stimulus has ceased to act on the retina, especially after looking at a bright object. An after-image at first increases in intensity and later fades away gradually. When the glowing filament of an electric bulb is gazed at for a few seconds and the eyes are closed or alternatively, a black surface is seen, the visual impression of the glowing filament persists. This is a case of positive after-image whose characteristics are the same as that of the original object. If after seeing the filament, a white surface is looked at, the after-image will be one

of a black filament, or in other words, a negative after-image. In the case of coloured objects, the positive after image will have the same colour and the negative after-image will be of a colour complementary to that of the object originally seen. The causation of a negative after-image is assumed to be due to fatigue of receptors sensitive to the original colour and a lowering of the threshold of receptors sensitive to the complementary colour.

Nerve pathways for pupillary and Near Reflexes:

The afferent pathway for the light reflex is along the visual pathway itself, upto a region anterior to the lateral geniculate body where the reflex fibres diverge away medially, to end on the pretectal nucleus (near the superior colliculus) of the same side. Thus, the optic tract of one side conveys light reflex fibres from the lateral retinal half of the same side and the medial retinal half of the opposite side, both of which make contact with the pretectal nucleus of the same side. The neurones of the pretectal nucleus which can be considered as internuncial neurones, establish contact with the 3rd nerve nuclei of both sides. The course of the efferent fibres arising from the oculomotor nuclei, have already been described (See elsewhere). It is evident from this that light thrown into one eye will bring about constriction of the pupil in both eyes – the effect in the eye stimulated being known as the direct light reflex and that in the opposite eye being known as the consensual light reflex. Lesions of the lateral geniculate body does not affect the light reflex at all (See also under Visual Pathway).

The afferent pathway for the reflex dilatation of the pupil, as under conditions of dim light or in any other reflex mechanism, follows the same route as for the constrictor pathway upto the superior colliculus from where fibres descend through the tegmentum of midbrain and the reticular formation of the brain stem to reach the spinal pupillodilator centre in the lateral horns of the last two cervical segments and the first four dorsal segments of the cord. For the efferent pathway – see Innervation of the Pupil.

Near or accommodation reflex: The afferent pathway is along the visual pathway itself upto the cerebral cortex. Long

association fibres convey impulses from the occipital lobe to area 8 in the frontal lobe for bringing about convergence of eyeballs. From area 8, motor fibres descend along the main pyramidal pathway to end on the 3rd nerve nucleus. The efferent pathway is along the 3rd nerve fibres to the extraocular muscles, especially the medial rectus. For ciliary muscle contraction and pupillo constriction, fibres travel from the occipital lobe to the pretectal region from where the course is as for the light reflex.

THE PHYSICAL CHARACTERISTICS OF SOUND

Sound is transmitted in the form of a wave motion through a solid or fluid or gaseous medium. Sound waves can be recorded graphically. Sounds can be divided into simple or pure tones and complex ones. A pure tone is one which, when recorded, is represented by a sine wave in mathematical terms. In other words, a vibrating particle generating a pure tone oscillates about a mean position at a steady rate. The excursions in the two directions from the mid position are equal. But the velocity of movement will change from moment to moment, being maximum when the particle is in the mean position and zero at either of the extreme positions (away from the mean position when there is a reversal in the direction of movement). Such a vibration is called a simple harmonic motion. To sum up, pure tones arise from a simple harmonic motion of vibrating particles of the conducting medium. The number of vibrations that occur in a unit of time (second) is the frequency of the tone. The extent to which the particle moves away from its mean position in either direction is the amplitude of the vibration. The greater the intensity of the sound wave (the energy transmitted) the greater will be the amplitude of vibration.

Complex tones are made up of a number of pure tones of different frequencies and intensities superposed over the others (algebraically summated). A graphic record of such a sound shows main waves of the lowest tonal frequency over which the components of higher frequencies are imposed. Even so, the wave form, albeit complicated with major and minor waves, shows a regular or rhythmical sequence. This is what

distinguishes a musical note from mere noise, which shows no regular order of waves. A graphic record of noise shows irregular fluctuations without any periodicity or regularity.

In the foregoing lines, the physical qualities or parameters of sound waves have been described. Corresponding to the frequency and amplitude (intensity), the subjective attributes of sound are pitch and loudness. It must be said that the pitch of a sound is mostly dependent on its frequency, though the intensity of the sound wave also determines it to a much less extent. Similarly, the loudness of a sound is determined by the energy transmitted in the sound wave and yet the frequency of the sound is also related to the loudness, though to a much less extent.

Whenever a musical instrument emits a note, not only a pure tone (fundamental or basic tone) is generated, but also tones whose frequencies are simple multiples of that of the fundamental tone are produced. These are the over tones or harmonics. Each musical instrument differs from the others in that the number of overtones that arise differs from one instrument to another, while the fundamental is the same. It is on account of this fact that the note delivered by one instrument can be recognised from that of another. In popular terms, each musical instrument produces a note which is of a different quality or timbre (another subjective attribute like pitch and loudness). Likewise, the human voice (that of a particular person) can be recognised because of its quality.

In the last century and in the earlier decades of the present century, the function of the ear as an analyser of sound waves was investigated using pure continuous tones. Nowadays, more sophisticated stimuli like sound pips (short trains of sound waves) of any chosen frequency are employed. The aural analysis of complex tonal patterns has yet to be unravelled.

THE PHYSIOLOGY OF HEARING

The ear analyses the various sounds falling on it in terms of their subjective attributes like pitch, loudness and quality (several attributes of sound) and sends impulses coding information about

these to the higher levels in the auditory pathways and eventually to the cortex. Sound waves reach the ear as waves of compression and rarefaction in the air surrounding the head. The ear has two mutually contradictory properties — resonance and damping. In other words, it shows neither inertia in the onset of its response to sound waves nor momentum, since its activity stops immediately after the sound stimulus ceases.

Anatomically, the peripheral hearing apparatus consists of the external ear, the middle ear or tympanum and the inner ear whose auditory part is the cochlea.

The external ear consists of the pinna or the lobe of the ear and the external auditory meatus which is 2.5 cm. long and 0.7 cm wide. Its inner part (inner $\frac{2}{3}$ rds) is in the temporal bone and is closed medially by the tympanic membrane or the drum. The outer part of the meatus is cartilagenous. The pinna is cartilaginous and has an irregular shape. Though said to be not important in man, yet the absence of the pinna is not advantageous. (see localisation of the direction of the source of sound). The external ear has a natural frequency of about 4300 cps. and so it amplifies sounds of frequencies close to that natural to itself. The pinna also directs sounds into the ear when they have frequencies greater than 6000 cps. Larger waves of sound may be obstructed. The elephant which has large ears can direct sounds of very low frequencies into the ear by moving its lobes. The horse is said to have about 17 muscles in the lobe of its ear which enable it to turn the ear in any direction.

The meatus protects the ear drum from injury and prevents the entry of insects and large particles of dust by means of hairs and a waxy secretion (cerumen) elaborated by sebaceous-like glands in the meatus. The air in the meatus and in contact with the drum is also kept warm and moist in order that the drum can be maintained in a healthy condition. The external meatus forms a S-shaped canal, at first directed medially, forwards and slightly upwards, then medially backwards and upwards and finally medially forwards and slightly downwards. The canal can be straightened in order to see the drum by pulling the pinna backwards and upwards.

The tympanic membrane or the drum is fixed in a sulcus in the meatus. It is elliptical in shape — 10 mm supero-inferiorly, 9 mm transversely and 0.1 mm in thickness. It is placed obliquely in the meatus and from above it slopes downwards and inwards to meet the floor of the meatus at an acute angle. It is funnel-shaped with its apical portion pointing into the middle ear. It is a pearly white in appearance. The manubrium of the malleus is attached radially to the drum and can be seen through it. The drum has a total area of about 60 sq mm though only $\frac{1}{3}$ of it vibrates in response to sound waves. Antero-superiorly it is somewhat loosely attached to the meatus (*membrana flaccida*). The rest of the drum is held under tension (*membrana tensa*). Externally, the drum is covered by skin and internally by simple squamous epithelium. In between, a system of radial and circular elastic fibres provides a framework of support. The drum is highly sensitive, responding to aerial vibrations of as little as that of the diameter of a hydrogen atom. It has very little inertia and is highly damped.

The tympanum or middle ear is roughly quadrilateral (in frontal section) — 15 x 5 x 2 mm and lodged in the petrous part of the temporal bone. Its walls are lined with a mucous membrane, ciliated except on the external wall where it covers the tympanic membrane. The internal wall is bony, having a promontory in it formed by the base of the spiral canal of the cochlea. Towards the rear of the promontory are two openings by which the middle ear 'communicates' with the inner ear. The upper opening is the oval window (*fenestra ovalis*) and the oval base or foot plate of the stapes is attached to the margin of the window by means of the annular ligament which is narrow and thick postero-inferiorly and broad and thin antero-superiorly. The lower opening — *fenestra tympanum*, *fenestra rotunda*, *fenestra cochlearis* — commonly known as the round window is covered by a membrane. Anteriorly, the middle ear communicates with the pharynx through the eustachian tube. The posterior and upper parts of the middle ear are connected with the mastoid air cells.

There is a chain of ossicles extending from the tympanic membrane to the oval window. Together they weigh only

55 mgm and no one is more than 10 mm in its greatest dimension. The manubrium of the malleus (hammer) is attached to the tympanic membrane. Its head articulates with the incus (anvil) whose long process in turn articulates with the head of the stapes (stirrup) whose base (or footplate) fits into the oval window. The foot plate of the stapes can rotate around an axis passing between its anterior $\frac{2}{3}$ rds and the posterior $\frac{1}{3}$ rd, as happens when loud sounds fall on the ear. (see below).

There are two small muscles in the middle ear — the tensor tympani and the stapedius (the smallest muscles in the body). The tensor tympani arises in a bony canal above the eustachian tube and is inserted into the manubrium of the malleus. The stapedius arises in the medial wall and is inserted into the neck of the stapes. The tensor tympani is supplied by a twig from the V nerve and the stapedius by a branch of the VII nerve.

The main function of the middle ear is to convey sound vibrations from the external ear into the inner ear. The ossicles are responsible for the transmission of sound waves from the tympanic membrane to the inner ear. If the chain is broken or becomes rigid due to disease, the threshold of sensitivity rises by 60 db. The chain moves as a whole. When the manubrium moves inwards, the head of the malleus and the body of the incus move outward and the long process of the incus and the stapes move inward. The base of the stapes is pushed in and out of the oval window like a door hinged along a line passing through its posterior margin. When loud noises fall on the ear, the stapes rotates on its transverse axis and thus protects the inner ear. In conducting sounds, the ossicular chain transfers the force or pressure of aerial vibration exerted on the drum of 60 sq. mm area (but effective area is only $\frac{2}{3}$ rds of this) to a much smaller area of the footplate (3 sq. mm). Because of 1) a mechanical advantage at the malleo-incudal joint of $\frac{3}{2}$ and 2) frictional losses in middle ear amounting to half the energy transmitted, the concentration of pressure is only tenfold ($60 \times \frac{2}{3} \times \frac{1}{3} \times \frac{3}{2} \times \frac{1}{2}$) at the oval window. This amplification is necessary because the impedance or resistance offered by air to the transmission of sound waves is much less than that of fluids. Thus, the pressure on the drum is concentrated or amplified 10 times at the oval

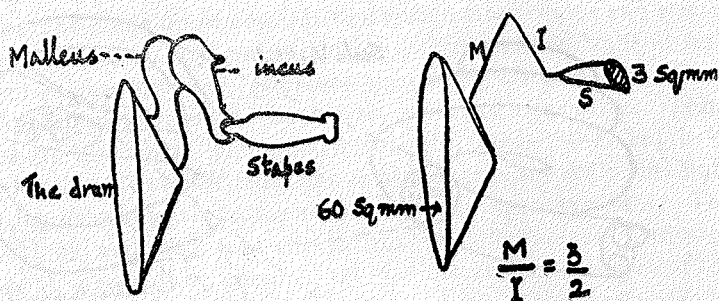


Fig. 73. Impedance Matching in Mipple Ear

window (fig. 73) in order that the low impedance of air is matched with the much higher one of the perilymph in the inner ear.

The intra-aural muscles have opposite effects on the base of the stapes. The stapedius tends to pull the stapes out of the oval window. The tensor tympani pulls the manubrium inwards and thereby pushes the stapes into the oval window. When both muscles contract at the same time, the ossicular chain is shortened and the tension on the tympanic membrane is raised. When low pitched sounds of less than 1000 cps and of great intensity fall on the ear, they reflexly bring about the simultaneous contraction of the two muscles which results in blocking of conduction of these sounds into the inner ear. This is a protective mechanism since these tones are harmful to the delicate structures in the inner ear. On the contrary, medium and high pitched sounds may be favoured by the reflex contraction of the muscles.

Functions of the Eustachian tube : It is opened by yawning, swallowing and Valsalva's manoeuvre (forcible expiratory effort with mouth and nose closed). When the eustachian tube is closed by inflammation or as it occurs in a rapid descent or ascent in an air plane, the pressures on the two sides of the tympanic membrane are unequal and hearing is depressed.

The inner ear is the most essential part of the auditory apparatus. The cochlear part is for hearing and the labyrinth for equilibrium.

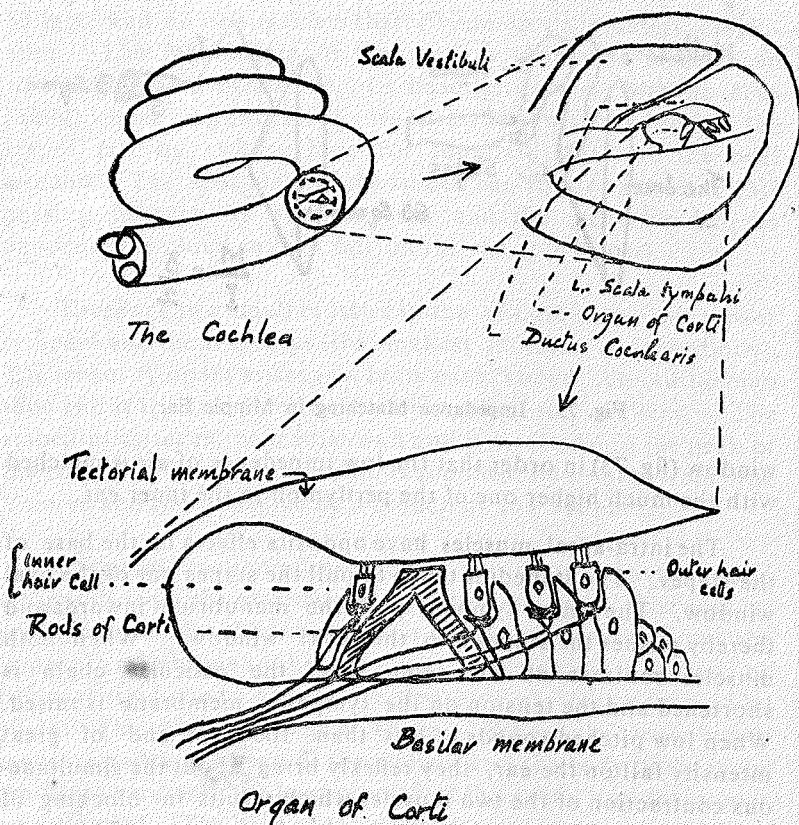


Fig. 74. The Inner Ear

The cochlea (fig. 74) is so named, as it resembles the shell of a snail. It is a coiled or spiral tube wound around a bony axis, conical in shape and known as the modiolus. The cochlea points laterally and forwards in the head. It measures about 5 mm in height and is 9 mm. across at its base (first turn — 6 mm. diameter; 2nd turn — 4 mm. in diameter). The human cochlea has $2\frac{1}{2}$ turns, while the guinea pig cochlea consists of 4 turns. The modiolus exhibits a bony shelf running spirally around it and projecting into the cochlear tube throughout its length. It is known as the spiral bony lamina and at its free edge it provides attachment to the inner margin of the well developed basilar

membrane made up of connective tissue, elastic fibres and numerous nerve fibres are embedded in it. The Reissner's membrane which is very delicate, stretches across the cochlear tube from the modiolus towards the outer wall of the cochlear tube. Thus, there are three parallel compartments throughout the length of the cochlea. These are from above downwards the scala vestibuli, the ductus cochlearis (scala media) and the scala tympani. The uppermost and the lowest compartments communicate with each other by means of an opening, the helicotrema at the apex of the cochlea and these are filled with perilymph. The scala media contains endolymph which may be secreted by the pigmented and vascular tissue, the stria vascularis, situated in its outer wall. The basilar membrane is narrow ($100\ \mu$) at the base of the cochlea but widens out gradually towards the apex where it is $500\ \mu$ wide. It is about 3 cm in length. The external spiral ligament by which the basilar membrane is attached to the outer wall of the scala media is thick, narrow and triangular in cross-section at the base of the cochlea but wider and thinner at the apex. The dimensional characteristics of the basilar membrane and the external spiral lamina are important in determining its mechanical response to sound waves incident on the ear. Resting on the upper surface of the basilar membrane all along its length is the spiral organ of Corti. (Fig. 74) It is built on the two sides of the tunnel of Corti which (tunnel) is made up of two rows of stiff cells (the pillars of Corti) which are separated at their basal ends which rest on the basilar membrane but meet each other at their upper ends. The floor of the tunnel is narrow ($50\ \mu$) at its commencement and wide ($100\ \mu$) at its end. On the inner aspect of the tunnel — facing the modiolus — a single row of hair cells are present. These rest in cup-shaped depressions in the bodies of cells, the Deiter cells, which stand on the basilar membrane. Covering the outer aspect of the tunnel are four parallel rows of hair cells, supported by Deiter cells. The cilia or hairs of the hair cells point into the ductus cochlearis and are embedded in the tectorial membrane which itself is attached along the inner edge to the bony spiral lamina. Its other edge is free. The tectorial membrane is paddle-shaped in cross section and is made of jelly-like material incorporating elastic and connective tissue fibres. There are about 3500 inner hair cells and 20,000 outer hair cells. The fibres of the auditory nerve which are given

off to the hair cells run from the modiolus, in the substance of the basilar membrane towards the hair cells. Those terminating at the outer hair cells reach them by crossing the floor of the tunnel of corti.

Conduction of sound waves : Whenever a wave of compression due to aerial vibration impinges on the ear, the drum moves inwards and as a consequence, the footplate of the stapes moves into the scala vestibuli whose basal end is at the oval window. The perilymph in the scala vestibuli is displaced towards the helicotrema. But, if the pressure wave is sudden in onset, the rise in pressure in the perilymph of the scala vestibuli is transmitted through the thin Reissner's membrane to the endolymph in the ductus cochlearis (scala media) and as a result, the basilar membrane is displaced downwards towards the scala tympani. The basilar membrane carries with it the organ of Corti and the tectorial membrane. In the meanwhile, the pressure wave in the scala vestibuli travels towards the helicotrema and down the scala tympani to cause bulging of the round window membrane into the middle ear.

When the footplate of the stapes moves out of the oval window as a result of a wave of rarefaction (succeeding the compression wave), a movement of the basilar membrane in the upward direction will occur through a chain of events but in a reverse direction to that referred to above. The round window membrane is sucked into the scala tympani.

The inner edges of the basilar membrane and the tectorial membrane are attached respectively, to the lower and the upper lips of the bony spiral lamina. But the lines of attachment of the two membranes do not lie exactly one below the other. The tectorial membrane has its inner edge nearer to the modiolus than the basilar membrane. Thus, when the two structures move together in response to sound waves, either downwards or upwards, there is a shearing action on the hair cells with the hairs bent towards the modiolus or away from it respectively. It is the bending of the cilia towards the modiolus that is responsible for the excitation of the hair cells.

Schematically the transmission of sound waves can be represented thus :

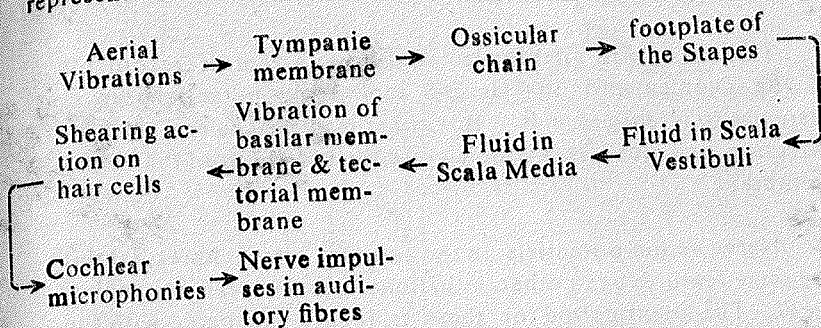


Fig. 75

Electrical activity in the cochlea: There is a steady potential difference of about 80 mv. between the endolymphatic space (negative to the rest of cochlear interior) and the rest of the cochlear interior – the perilymphatic space. The cellular origin of this is yet to be identified. The hair cells may probably be responsible for this phenomenon. It is to be remembered that the endolymph has the characteristics of intracellular fluid and the endolymphatic potential is analagous to the membrane potential of an excitable cell—muscle fibre and nerve cell. But the ionic composition (high potassium concentration) does not account for this potential.

In 1930, Wever and Bray discovered the cochlear microphonics which have a wave pattern when recorded, reflecting the frequency of the tonal stimulus and its intensity. In the cat (under anaesthesia), an electrode was placed on the cochlea or round window and another electrode elsewhere on the head and the two connected through an amplifier to a speaker. When words were spoken into the cat's ear, they could be reproduced by the speaker. A wave-like record could be seen on the oscilloscope screen if the speaker were replaced by a cathode ray oscilloscope. The cuticular surfaces of the hair cells of the cochlea are taken to be the origin of these alternating potentials. The first half of the negative phase of each wave of the cochlear microphonics appears to link the mechanical displacement downwards of the

basilar membrane with the excitation of the auditory nerve fibres and the nerve action potentials.

There is a third kind of electrical activity that is recordable in the cochlea and that is the summing potential seen in response to intense sounds. It is either positive or negative in its direction and denotes asymmetry in the behaviour of the basilar membrane.

Nerve action potentials in the auditory nerve fibres exhibit the same features as in other situations (see cochlear microphonics). The latent period for these is longer compared with the cochlear microphonics and unlike the latter, are 'all or nothing' in character. At the most, they correspond in frequency with incident tones upto 3000 cps. The clues for the appreciation of loudness seem to be the frequency of discharge of impulses in individual fibres and the number of active fibres,

THE AUDITORY PATHWAY

The hair cells of the cochlea (both inner and outer) are innervated by the peripheral processes of cells of the spiral ganglion situated in the bony modiolus of the cochlea. The external hair cells have only afferent fibres in contact with them. These convey impulses generated in the hair cells to the higher levels in the auditory pathway. The inner hair cells on the other hand, have afferent fibres in addition to the final terminations of the efferent fibres from the opposite superior olivary complex of nuclei. In general, every afferent fibre given off to the hair cells need not always contact the hair cells nearest to its point of origin (radial fibres) in the cochlea, but may travel up or down (towards the helicotrema or base of the cochlea) to end on more distant hair cells (spiral fibres).

The central processes of the ganglion cells are all collected in the basal turn of the cochlea to form a compact bundle, the auditory division of the 8th cranial nerve or the statoacoustic nerve which runs towards the medulla in the internal acoustic meatus. Situated in close relationship to the restiform body are the two divisions of the cochlear nucleus, the dorsal and the

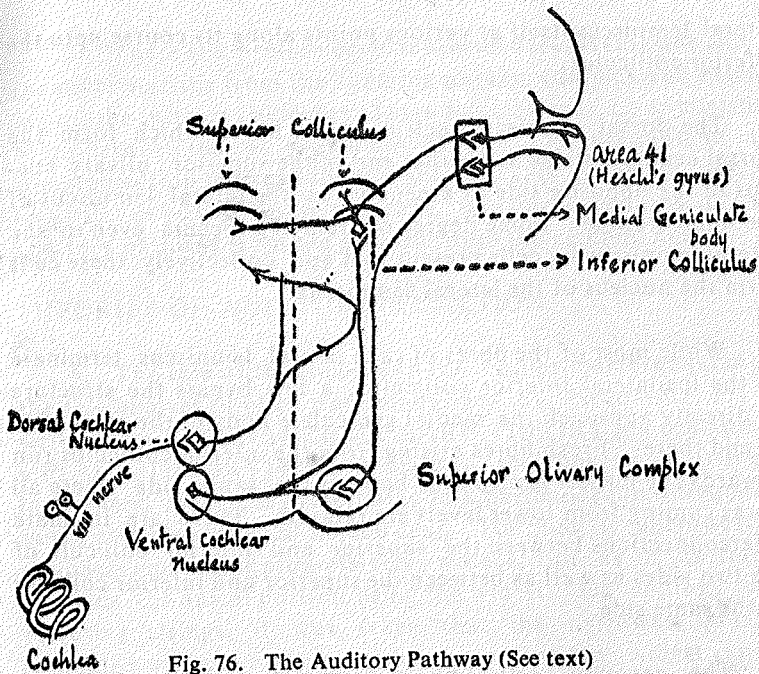


Fig. 76. The Auditory Pathway (See text)

ventral masses. Each auditory nerve fibre divides into two branches – one meant for the dorsal nucleus and the other for the ventral nucleus. Before terminating on the cells of the cochlear nucleus (either division), each branch of auditory nerve fibre divides again into 13 twigs, each one of which ends in one group of cells in either of the cochlear nuclei. Some of the second order fibres arising from the ventral cochlear nucleus cross over to the opposite side. Others approach the superior olivary nuclear group of the same side. As they do so, the second order fibres from the ventral cochlear nucleus form the trapezoid body which is anatomically a distinct structure. The 2nd order of fibres from the ventral cochlear nucleus end on cells in the superior olivary nucleus of the same and the opposite side where a fresh set of fibres arise and ascend up, forming the lateral lemniscus. Some second order fibres may undergo relaying by certain cells in the trapezoid body itself. The majority of the fibres of lateral lemniscus ascend to the inferior colliculus to terminate in that body. It has been seen that there is a crossing over of fibres from the

lateral lemniscus itself at various points along its course upto the inferior colliculus.

The dorsal cochlear nucleus emits fibres which form the dorsal acoustic striae and either end in the superior olivary nucleus of the opposite side or ascend up in the lateral lemniscus of the opposite side. Some degree of relaying occurs even in the lateral lemniscus by cells present in it and collectively these cells form the nucleus of the lateral lemniscus.

While most of the fibres of each lateral lemniscus terminate in the ipsilateral inferior colliculus, a few bypass the structure to directly approach the medial geniculate body of the same side to end there. Fresh fibres arising from the inferior colliculus run towards the medial geniculate body of the same side where all fibres coming from lower levels are relayed. There are intimate interconnections between the superior and inferior colliculi of the two sides as well as between the superior and inferior colliculi of the same side.

The geniculo-cortical fibres form the auditory radiations which finally end in the transverse or Heschl's gyrus situated in the middle part of superior temporal convolution. This cortical region is denoted by the numbers 41 and 42 as given by Brodmann and is also called the primary auditory cortical area. The adjacent portions of the superior temporal convolution constitute the auditory association areas.

Attention must be drawn to certain important anatomical peculiarities of the auditory pathway described above.

1. The number of relaying cells increases at each level and this is known as the unrolling of the cochlea many times in the higher reaches of the pathway.

2. Fibres of different orders run together unlike in other sensory pathways wherein the first order fibres lie at a lower level than the 2nd order ones and so on. In addition, while all the other afferent pathways are made of three or four neuronal links, in the auditory pathway there seems to be more links than four.

3. There is a profuse decussation of fibres from one side to the other starting from the superior olivary complex and extending till the inferior colliculus. There are, however, no commissural fibres between the two geniculate bodies. On account of the communication between the two sides of this pathway, hearing loss will not be of a severe degree in unilateral lesions of the auditory pathway from the cochlea upto the cerebral cortex.

THEORIES OF AUDITORY FUNCTION

I. The role of the cochlea or the basilar membrane (bm) as the sole analyser of pitch was emphasized by Helmholtz in his well-known RESONANCE OR HARP THEORY (an example of a PLACE THEORY). He visualised the bm as a stringed instrument, each string resonating to a particular tonal frequency in the audible range (20-20,000 cps). The bm is narrowest at the basal end and it progressively widens out as it is traced upwards, the apical portion being the widest. On analogy with vibrating strings, it was taken that the narrowest portion resonated with the highest audible tones and the widest apical region to the lowest tones, with the intermediate regions responding to medium frequencies.

Much anatomical, experimental and pathological evidence accumulated subsequently in support of the above concept. Birds which have narrow audibility ranges were found to have short basilar membrane. Experimental studies on guinea pigs with prolonged and intense stimulation with particular tones, showed damage in strictly localised areas in the bm. Discrete or small lesions in the guinea pig bm rendered the ear insensitive to certain tones only. Post-mortem examination of the basilar membranes of boiler-makers showed that the basal parts only were damaged. This was correlated with the fact that these people were subjected to intense high-pitched sounds all their lives.

Resonance, of a strictly limited area in the bm, to any tone is the hall mark of this theory. The analyser function accordingly is relegated to the receptor apparatus, the cerebral cortex merely locating the active or resonating area in the bm which is topologically represented in the auditory cortex.

II. THE TELEPHONE THEORY of Rutherford (frequency principle) elevates tonal discrimination to the level of cerebral cortex, the bm having a passive role. The bm is assumed to vibrate at the same rate as the frequency of the tone falling on the ear, in the manner of the diaphragm of a telephone receiver. Impulses are thereby generated in the auditory nerve fibres at the same rate as the number of vibrations per second in the stimulating sound. This hypothesis is adequate to account for appreciation of sounds upto 1000 cps. Theoretically speaking, no nerve fibre can conduct more than a thousand impulses per second, because of the absolutely refractory phase of nearly a millisecond between one impulse and another. The VOLLEY THEORY of Wever was proposed to meet this objection. It is presumed that each nerve fibre does not respond to every vibration of a sound of more than 1000 cps but is excited by one out of two or three vibrations. Even so, this view serves to explain sensitivity of the ear only to tones below 2000 or 3000 cps but not higher.

III. Von Békésy made a crucial experiment leading to the rejection of the concept of localized resonance in the basilar membrane in response to sounds. He made short incisions in the bm parallel to its length. But the wounds did not gape open in the transverse direction as would happen if the transverse fibres of the bm were held under tension. Thus it was conclusively proved that each tone could not activate a particular segment or bit of the bm in isolation from the rest of the membrane, as was required by the resonance hypothesis of Helmholtz. Of much greater significance was the work of the same author by way of his remarkable studies of the mechanical properties of the cochlea in artificial models as well as living ears (of guinea-pigs) and the ears of human cadavers immediately after death. He saw travelling wave patterns (fig 77) in the bm in response to tones introduced into the ear. Each tone gave rise to a wave which travelled from the base towards the apex, the amplitude being small at the commencement but gradually increasing and eventually reaching a maximum at a region of the bm which was specific for each tone. After this, the wave suddenly dwindled in size. The maximum for low tones was at the apex and it shifted towards the base as the frequency of the tone was raised. While the spacing of the low tones was liberal in the uppermost turn, the medium

and higher tones were represented in a more and more crowded manner towards the basal turn, like a logarithmic scale. In pulses were set up in the nerve fibres in contact with the region of maximum disturbance in the bm. Two tones which could just be distinguished from each other had regions of maxima which overlapped at the edges but were not separate as required by the Resonance Theory. This implied that the tonal analysis in the bm was not very accurate. Greater precision or sharpness was achieved progressively as impulses travelled to higher levels in the auditory pathway as Whitfield, Galambos and others showed recently. The value of Von Bekesy's work was recognised by the award of the Nobel prize.

Since low tones threw nearly the whole of the bm into vibration — their maxima being near the apex — Rutherford's theory could be valid, in effect, to this extent only. With medium and high tones, smaller lengths of the bm were affected in the basal portions, the apical regions being left out completely.

The present position is that both the older concepts are acceptable though in a very much modified form. The idea of strict resonance or of completely passive behaviour of the bm has to be thrown out in the light of Bekesy's work. To sum up, the frequency principle in a much emasculated way may explain responses to low tones and the Place Principle is substantiated in respect of medium and high tones.

CENTRAL ANALYSIS OF TONES

The auditory pathway exhibits certain special features. The number of nerve units increases gradually as the pathway is traced upwards. Not all these are responsive to stimuli. Though the absolute number of active units increases, their proportion diminishes. There are many units above the level of the cochlear nucleus which exhibit spontaneous discharges and their activity may actually be inhibited by tonal stimuli. Thirdly, there are units which are silent whether tonal stimuli are present or not. Which units are activated, which are inhibited and which are unaffected, will depend on the frequency and the intensity of the tones falling on the ear.

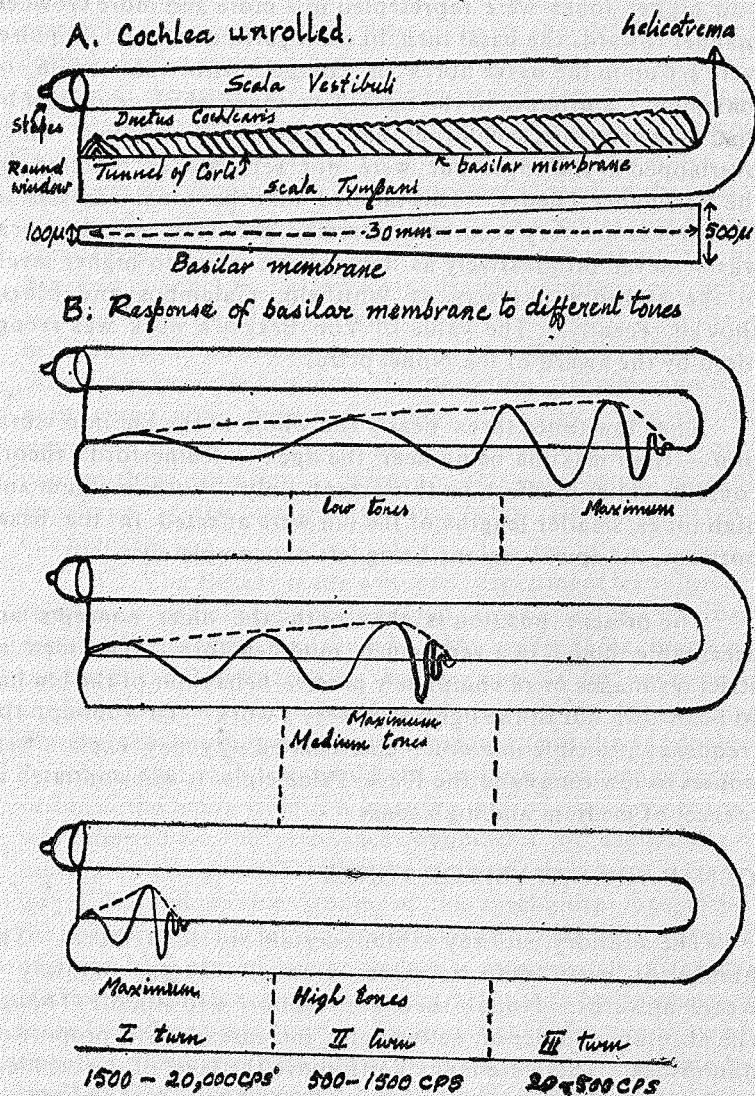


Fig. 77. The Travelling Wave Concept

There is a regular topologic (spatial representation of the basilar membrane) and tonotopic (representation of individual

tones) at each level of the auditory pathway. The work of several investigators has established this fact in the experimental animals cat, dog and the monkey. In man, the cortical areas of Brodmann - 41 and 42 in the superior temporal gyrus - have been found to exhibit potentials evoked by tonal excitation.

Von Bekesy has convincingly shown that since the envelope of the travelling wave pattern (fig. 77) has a rounded or somewhat flattened maximum, the peripheral analysis in the end organ is at best an approximate one only. Further improvement or sharpening effect, as it is called, is achieved progressively at higher and higher levels upto the cortex. In lower animals, auditory cortex seems to be necessary for remembering patterns of tones rather than for analysis of individual tones which is subserved by the lower centres. Much neurophysiological evidence has accrued in the recent past in favour of the above mentioned conclusions from the studies of Whitfield, Galambos, Davis and others involving the recording of potentials at various levels in the auditory pathway.

Unilateral lesions of the auditory pathway at any level do not result in hearing defects of a marked degree, the losses being very slight. This is shown to be due to bilateral representation of each cochlea as manifested by the profuse crossing over of fibres from each side, from the medullary level upwards upto the level of the inferior colliculus.

PERCEPTION OF LOUDNESS

The loudness of a tone depends on the number of auditory nerve fibres activated by it. When the intensity of a sound is raised, the travelling wave exhibits greater amplitude in its individual waves though its spatial characteristics as regards the basilar membrane remain the same as at lower intensities. It is taken for granted that for a nerve fibre to be stimulated (at the region of maximum displacement in the travelling wave), the basilar membrane should be displaced beyond a certain distance from its resting position (in the absence of sound). When the wave is of a greater amplitude, as with an intense sound, more nerve fibres will be excited since a wider segment of the bm (at the region of

the maximum) will now be shifted in excess of the minimum displacement necessary for excitation of the nerve fibres and hence many more fibres will be activated. The sensorium (cortex) will therefore receive a greater number of impulses, quantitatively speaking, though through more fibres, in a unit of time. The more intense the fusillade of impulses from the bm, the greater will be the loudness of the sound. It also happens that each individual fibre may transmit more impulses per unit time for louder sounds than for less loud sounds. This feature also may partly account for the appreciation of loudness.

MASKING

A loud sound masks or prevents the hearing of a weaker or fainter one. Loud low-pitched sounds have a greater masking effect than those of high pitch. Tones which lie within a narrow range of frequencies on either side of a given tone, are effective in masking the particular tone.

Masking provides a convenient way of measuring noise levels. An electrically produced sound (as by an audiometer) is increased in intensity gradually till it is just heard by a normal person in noisy surroundings. Then the intensity of the given tone measures the masking effect of the noise. Masking may be responsible for a person with middle ear deafness hearing better, amidst noise. A normal person, talking to such a deaf subject, unconsciously raises his voice (in noisy surroundings) so that the latter can hear better.

Masking of one sound by another is attributed to overlapping of the two zones of response (in respect of the masking tone and the masked tone) in the basilar membrane. This view is based on the Helmholtz's harp or resonance theory and finds adequate support from Bekesy's work also. This implies that masking is in the end organ of hearing. On the other hand, a sound fed into one ear can mask that introduced into the other. This indicates a central mechanism too. The phenomenon of masking has a practical application in that, when one ear is being clinically examined, the other is rendered inactive by masking. But the threshold for hearing, in the ear being examined, is raised.

The direction of the source of sound: When a source of sound on one side of the head sends waves to both the ears, these reach one ear (the nearer one) earlier than the other (farther one). This causes the volley of nerve impulses generated in the nearer ear to travel up the ipsilateral auditory pathway in advance of the volley set up in the opposite ear. The different instants at which the two volleys ascending up the nerve pathways reach corresponding levels on the two sides give the clue as to which side of the head is nearer to the source of sound and thus enables its localisation. This mode of localisation holds good for sounds of brief duration or even of an intermittent nature. When the source of sound is in the midline, the sound waves reach the two ears simultaneously, whether the source is in front or at the back of the head. Nerve impulses arise in the two ears without any time lag between the two sides. This brings about the placing of the source of sound in the midline. In the case of sounds produced from a source behind the head, the pinnae of the ears may block the waves of high tones and this blocking effect provides a means for locating the direction of such sounds behind the head.

What has been mentioned hitherto does not apply for continuous sounds. The wave nature of sound helps in this connection. Each sound wave strikes the ear drum at a particular stage or moment in its cycle of changes. This is known as the phase in the parlance of physicists and mathematicians. Thus, a continuous sound originating from a source placed to one side of the head arrives at the two ears at different phases. This phase difference is perceived by the auditory system. But this mode of detection of the source of sound is applicable only to tones below 8000 cps. For higher tones this method fails, thereby accounting for the inability of the human ear to locate sources of high pitched sounds for which the differences in the loudness experienced in the two ears may, to a small extent, be of use. This is so because the head blocks off high pitched sounds arising from one side of the head. Loud low pitched pure tones (less than 1000 cps) are not affected by the presence of the head whose dimensions are less than that of the wavelength of these sounds and thus there cannot be a 'sound shadow' cast by the head. Complex sounds made up of low and high pitched sounds are however located as regards their source

because the pinnae and the head can act as barriers to the higher components and help to find the source.

Beats or mutual interference among sound waves: If two tones of nearly the same frequency are simultaneously applied to the ear, they may meet in the opposite phase at one instant and in the same phase at another. So, alternate interference (or suppression) and reinforcement—waning and waxing—occurs. At a certain frequency, this gives rise to a throbbing unpleasant sensation (similar to flicker in vision). The reinforcement is called a beat. Number of beats per second corresponds to the difference between the two tonal frequencies. If the number of beats/sec is too low, it may not be perceived. If it is too high, than a harmonious blend—a difference tone, results. The frequency at which beats disappear and at which they becomes most unpleasant, depends on the pitch of the lower tone. Beats can be explained on the basis of resonance theory—Overlapping of two neighbouring (and vibrating) sections of the basilar membrane during beats. Greater the difference between the two tones, more wide apart on the bm they will be represented and there is less chance of beats being caused. Greater the intensity of the two tones, greater will be the chance of overlap, as the respective resonant areas for the two tones will be wider at higher intensities. Beats will be caused with greater ease for the same intensity for lower tones than for higher ones. Weak low tones of nearly same frequency, if inaudible separately, will be heard better when applied together to the ear.

Practical application: In mines, fire damp (methane) being lighter, transmits sounds faster than air. Two long tubes are filled, one with air and the other with the suspected mine air and they are blown together. If one contains fire damp, then beats will be heard, the rate depending on the concentration of the gas.

TESTS FOR ACUITY OF HEARING

Initially, as a crude means, the ability to hear ordinary conversational speech is gauged. Additional information can be obtained by finding out at what distance whispers can be heard. Quantitative information can be obtained by the watch test.

Finding the maximum distance at which the ticking of a watch can be heard by each ear and comparing it with that of the observer, subject to the proviso that the observer has normal hearing, can give an idea of the acuity of hearing.

Two reliable tests, making use of a tuning fork, have been in vogue for distinguishing between normal hearing and deafness, as well as between the two kinds of deafness.

Rinne's test: A tuning fork is set into vibration and its stem is placed on the mastoid process. When the hum of the fork is no longer audible, the fork is brought opposite the external meatus. If there is no hearing loss, the sound will now be heard, proving that air conduction of sound is better than bone conduction. In the presence of a defect, the sound will not be heard. However in a silent or sound-proof room, both air conducted and bone conducted sounds are heard for equal lengths of time. Since surrounding noises mask air conducted sounds, bone conducted sounds are heard longer by subjects having conduction (middle ear) deafness. In cases of nerve deafness, both modes of conduction are affected.

Weber's test: The stem of the vibrating fork is placed on the middle of the forehead. If both ears are normal, hearing will be to equal degrees on both sides. If there is conduction deafness, on one side, the sound is heard better on the affected side, as bone conduction is more efficient than air conduction. Of course, with bilateral conduction deafness, hearing loss will be to same extent on both sides. Nerve deafness will affect both routes of transmission.

These observations are valid only for a room filled with ordinary noises. In a sound-proof environment, in unilateral middle ear disease, both ears will hear equally, as there are no neighbouring noises to mask air transmitted sounds.

Audiometry: The audiometer is an instrument used to determine the threshold intensity for any tone in the audibility range. In practice, the intensity levels is measured in decibels. The logarithm of the ratio between the energy level of a sound and

that of the just perceptible or threshold level of the same yields the large unit bel, named after Graham Bell. A tenth of a bel is the decibel. On a squared paper, the tones are represented horizontally on a logarithmic scale. The zero line (horizontal) gives the average threshold for various tones for a large number of normal subjects. There are a number of lines below the zero line and parallel to it. Each line represents a ten decibel loss in loudness compared to the one above it. The thresholds for about eight tones distributed in the functionally most useful part of the range of hearing are determined. Normal subjects should have their audiogram, the line joining the different threshold points, very close to the base line.

In middle ear deafness, the curve is much displaced downwards from the zero line for the lower frequencies, but approaches the zero line for higher tones. In nerve deafness on the contrary, higher tones have raised (lower position of the curve) thresholds, the lower ones are not much affected. Nerve deafness is a symptom of old age. As age advances, the ear gradually loses its sensitivity to the higher tones, starting from 20,000 cps and affecting lower tones. The commonest cause of middle ear or conduction deafness is chronic inflammation of the middle ear involving the ossicular chain. Otosclerosis is a degenerative process which also leads to conduction deafness.

In middle ear deafness in human subjects, there is a hearing loss of 60 db affecting the lower and middle tones. In the dog, loss of the cerebral auditory area causes a deficit of 2-5 db., the same as occurs when one cochlea is destroyed. Lesions placed in one auditory area and also in the cochlea of the same or opposite side, cause a hearing loss of 15 db. The greatest effect of 75 db loss was seen with bilateral excision of the cortical areas.

CHEMICAL SENSES

Taste, smell and general chemical sensibility (common sensibility) are the three chemical senses. Of these, general chemical sensibility was the earliest to develop and was present from the

dawn of life in the unicellular organisms like the amoeba which tried to escape adverse chemical (irritant) environment. Later, it showed evolution or differentiation into taste and smell (taste at a distance) in the higher forms of life. While smell has been considered to have become vestigial in the human species, all the same, it is retained to a remarkable degree. Unpleasant or fragrant odours can be recognised even when the air contains particles responsible for them in very high dilution. General chemical sensibility is also retained by the higher animals and man. It is subserved by the 5th cranial nerve fibres in the mouth and the nose and these respond to irritant or pungent gases and food stuffs. Taste has a great biological significance. In animals and in young children, taste guides in the selection of a balanced diet from the nutritional point of view. In the human adult, it is somewhat of less value in this respect and capricious taste only makes a man a gourmet, blissfully oblivious of his nutritional needs.

PHYSIOLOGY OF TASTE

Taste is a complex sensation arising mainly from specific taste receptors and also on account of tactile, chemical and thermal stimuli arising in the mouth due to the presence of food (fig. 50).

Receptors: These are situated on the tongue, soft palate (not uvula), anterior faucial pillars, a few on the inside of the cheek and the under surface of the tongue. In the dorsum of the tongue these exist in association with the circumvallate papillae mainly, and also to an extent, with the foliate and fungiform types of papillae on the tongue. The taste bud consists of an oval cavity containing the sustentacular cells, filling it like the sections of an orange. In the central space are the gustatory cells which have minute hair-like processes which project upwards to lie in the opening of the taste bud (taste pore). The sensory fibres lie in contact with the hair cells at their lower poles.

The taste cells are stimulated only if the substances responsible for taste are dissolved in saliva. Taste sensitivity is depressed in conditions causing dryness of the mouth.

Chemical basis and classification of taste: Four primary tastes were thought to occur originally, viz — sweet, sour, salt and bitter. To these may be added metallic and alkaline tastes.

Sweetness is said to be due to presence of CH_2OH group in the molecular structure. All sugars have this group. Other non-sugar substances could be sweet if they have this group. The sour taste is due to the H^+ -ion. So, the more strongly ionising acids like HNO_3 , HCl and H_2SO_4 , are more sour than weakly ionising ones. But organic acids like acetic acid are as sour as the strong mineral acids. The cause is their lipid solubility. The salt taste is due to the metallic radicle, as two chlorides may taste differently. All alkaloids are bitter, though all bitter substances are not alkaloids. Strychnine is perhaps the most bitter substance known. Dulcine is one of the sweetest substances and saccharine is another, though these are non-carbohydrate (hence lacking CH_2OH group) substances.

Spatial distribution of taste modality: In childhood, taste buds are present over the entire dorsal surface of the tongue, but in the adult, the receptors are confined only to the tip and edges of the tongue. Each of the primary tastes is specially subserved by a definite part of the edge of the tongue. Sweetness is felt by the tip, the adjacent posterior part of the edge being responsible for saltishness. Still further backward is the region for sour or acid taste and the posteriormost part of the tongue subserves bitter taste. Even so, these regions are not exclusively devoted to the particular type of taste.

Taste disturbances: Ageusia means loss or depression of taste sensibility. Drugs like gymnema sylvestre abolish sweet and bitter tastes selectively, but not sour and salt tastes. Loss of taste should be unilateral, if the peripheral nerves only are involved. Bilateral loss is very rare.

Testing of taste sensibility: With the mouth open and the tongue put out so as not to touch any other part of the mouth, small quantities of the tasty substances should be placed on the dorsum of the tongue on one side of the midline. The subject should be instructed to indicate the taste by writing or in

any other way except orally, since uttering of words brings the non-lingual receptors also into activity by means of contact between the tongue and other parts of the mouth.

Fatigue and adaptation: The tongue gets adapted to a taste rapidly, especially in the case of sweet taste. Fatigue can also occur, as with intense and prolonged stimulation.

Complex taste experience can occur, as with the mixture of sweet and sour tastes. Flavour is a result of taste and smell sensations combined. In the presence of a nasal cold, it is said that a potato and onion taste alike.

Nervous pathway for taste: The lingual nerve subserves taste in the anterior $\frac{2}{3}$ of the tongue, the rest being supplied by the glossopharyngeal. The lingual fibres run in the chorda tympani (or greater superficial, rarely), the cells of origin being in the geniculate ganglion. The fibres of the ninth nerve arise from the petrosal ganglion.

The central processes of the ganglion cells of the two nerves enter pons and medulla along with the X nerve fibres (from epiglottis) and form the descending tractus solitarius and end in its nucleus. Fresh fibres arise in this nucleus and after crossing over to the opposite side run up with the medial lemniscal fibres to terminate in the arcuate nucleus, which is the medial-most part of the postero-ventro-medial nuclear mass of the thalamus. Thalamocortical fibres from the arcuate nucleus reach the lower end of the postcentral gyrus and the para-insular cortex. Since the cortical area for taste is in the general somatic sensory area, some consider the taste sensation as not a special sense.

OLFACTION

The sense of smell is a vestigial one in man who is a micro-omatic animal. In lower animals, the greater part of the cerebral cortex is devoted to the perception of smell, whereas in man, the olfactory cortex is confined to certain portions of the limbic lobe. The olfactory pathway is rather ill-defined, in contrast to other sensory pathways. Also, the thalamus is not a relay station in the pathway for smell.

The olfactory epithelium extends over 250 sq. mm, occupying the surface of the superior turbinate, the roof of the nasal cavity and the upper part of the septum of the nose. It is brownish yellow in colour. The histology of the olfactory mucous membrane is different from that of the epithelium of the rest of the nose. There are three types of cells. The supporting cells are tall and columnar and form a continuous surface with round or oval gaps in it through which the hair-like processes of the olfactory cells project and are thus exposed to the external environment. The olfactory cells are fusiform in shape with the hair bearing ends expanded and containing the olfactory vesicles which in turn have 6-8 granules, each of which give rise to a hair-like process. The olfactory cell is unique in that it is a modified nerve cell whose hair-like cilia can be equated to dendrites and its central process is an axon. This cell is the only example of a nerve cell which is exposed to the external environment directly. The third cell is the basal cell, conical in shape and lying near the basal end of the supporting cells. These are thought to replace by growth, the supporting cells, as they wear away.

Smell is considered as taste at a distance. Biologically, smell is useful in searching for food and mate, in addition to warning the animal about the approach of its predators. Even in man, while it is a disappearing faculty, yet the threshold for smell is very low. Some substances like artificial musk, can be smelt in a concentration of less than a billionth of a milligram in a cubic centimetre of air. The inspired air ordinarily, does not reach the roof of the nose which is bypassed. When an individual wants to detect a smell, a 'sniff' reflex results. This consists of a short sharp inspiration with an accompanying extension of the neck, in order to direct the inspiratory air straight towards the roof of the nose. For any odoriferous particle to excite the smell receptor, a preliminary condition is its solution in the secretion of the Bowman's glands which are situated in substantia propria. Some authors are of the opinion that the secretion of these glands have only a cleansing function. All the same, solubility in water and lipids seems to be an essential requisite for a substance to stimulate the olfactory cells. Some degree of spatial representation seems

to obtain in the olfactory surface of the nose. Water soluble substances appear to stimulate the anterior region, while the part behind responds to the action of lipid soluble particles.

Chemical constitution underlying smell: The higher members of a series of organic compounds are more potent than the lower ones. Thus, amyl alcohol is 10,000 times more powerful than methyl alcohol. Substances having atoms in the same column of the Periodic table (of Mendeljeff's) have similar smells eg.-chloroform, bromoform and iodoform. Contrarily, substances not related to each other may have the same smell. The position of a radicle like OH, CHO, CO and NO₂ (osmophoric) in a compound is more important than what the radicle is.

Threshold determination: This can be done with the use of an olfactometer (Zwaardemaker's) which consists of two glass tubes, one inside the other. The outer one has a lining of India rubber or beeswax or some other substance. One end of the inner tube is curved and narrow and this is kept in one nostril, the other nostril being closed. The subject breathes quietly throughout the procedure. The outer tube is gradually withdrawn away from the nostril so as to expose more and more of the inner aspect of it to the air current (inspired air), thereby increasing the concentration of the odoriferous substance in the air. The graduation on the outside of the inner tube is noted when the smell is just perceptible (threshold). Each division on the inner tube is 0.7 cms from its neighbouring one and the threshold is denoted in terms of 'olfacties'. One great drawback is that there is no control over the force of inspiration. So, the results are not strictly comparable. A more refined procedure is that of Elsbury and Levy, in which this defect is remedied.

From these determinations it has been found that substances like xylene, camphor and clove oil are detected in very high dilutions in the inspired air.

Classification of odours: Adrian has classified all substances with smell, into four categories: 1) Aromatic hydrocarbons 2) Paraffin hydrocarbons 3) Terpenes 4) Ethereal esters and ketones.

A more comprehensive classification of smells is as follows :

- 1) Ethereal odours – fruits, beeswax, ethers etc.
- 2) Aromatic or resinous odours – camphor, bitter almonds, cloves, asafoetida.
- 3) Fragrant or balsamic – flowers, flower essences and artificial perfumes.
- 4) Ambrosial – musk.
- 5) Garlic – onion, garlic, sulphurous compounds.
- 6) Burning odours – burning feathers, tobacco and roasted coffee.
- 7) Goat odours – caproic acid, sweat, ripe cheese.
- 8) Repulsive odours – hyocyamus, bed bug.
- 9) Nauseating – excrement, decaying meat and vegetable matter.

The exact mode of stimulation of the receptor is not known. Certain views are held in this regard. One is that odoriferous substances may inhibit certain enzymes in the receptor, in addition to undergoing a series of chemical transformations. The combined presence of the derivatives and the stage at which the changes are blocked, will give rise to the particular smell perception. This hypothesis leaves many things unexplained.

Adaptation and Fatigue : Both these phenomena are seen in the case of smell.

Loss of smell : This is a very rare condition and is called anosmia. Smell is lost in common cold. A permanent loss implies a lesion in the brain or an absence of the nerve of smell. In uncinate attacks, olfactory aura may occur.

In women, smell thresholds may be lowered just before and during menstrual periods. Albinos may lack the sense of smell, possibly because of the lack of the yellowish pigment.

The pungent odour of substances like ammonia arise out of stimulation of the V nerve endings. Smell, together with taste, gives rise to flavour. One smell can mask another. Contrary to popular notions, certain substances like chloroform are not

smelt but the vapours are actually tasted and give rise to a sweet 'smell' which should really be called taste.

The central processes of the olfactory cells are gathered together in twenty bundles (olfactory nerves) which pierce the cribriform plate of the ethmoid bone to reach the olfactory bulb. Here the primary neurone makes synaptic contact with the dendrites of the mitral cells (2nd order neurone) and those of the tufted cells which are considered to make contact with the opposite olfactory bulb. The region of contact between the receptor cells and the cells of the bulb, exhibits discrete spherical structures called the glomeruli. Many thousands of receptors make contact with a few of the mitral and tufted cells, thus showing convergence.

The olfactory fibres are non-medullated, but have neurilemmal coverings which merge with the coverings of the brain. Thus the perineural space which is continuous with the sub-arachnoid space, is exposed to the exterior, thereby providing a potential portal of entry for micro-organisms (infection).

The axons of the mitral cells and the tufted cells form the olfactory tract which runs backward to end as the olfactory tubercle, wherefrom three pathways diverge. The medial tract or olfactory gyrus merges with the para-olfactory area (gyrus subcallosus) which connects with the cingulum through the longitudinal striae. The lateral tract passes on to the amygdaloid nucleus, uncinate gyrus and the hippocampal gyrus. The pyriform area includes the uncinate gyrus and part of the lateral tract itself. The intermediate tract runs on to the anterior perforated substance.

The olfactory cortex consists of the parahippocampal gyrus, dentate gyrus, cingulate gyrus and anterior perforated substance. The olfactory cortex has connections with the prefrontal cortex and the midbrain nuclei. Other connections are also described. Some of these connections bring about autonomic responses to smell stimuli.

The anterior commissure conveys fibres from one bulb to its fellow on the opposite side. There is a third kind of cell (granule cell) in the olfactory bulb, which are believed to receive descending fibres from the olfactory cortex and in their turn, send fibres to end on the mitral cells. This channel may possibly provide some degree of control by the cortex of the receptor activity.

The olfactory cortex (rhinencephalon) is part of the limbic lobe. It takes part in the integration of emotional responses and general behaviour. The hippocampus and the cingulate gyrus receive fibres from the auditory and optic pathways also.

THE TISSUES

The component elements of the body are the tissues (formed cells), cementing substances and extracellular fluid. Each of these will be described separately.

The term tissue refers to a collection of cells usually alike in structural and functional characteristics. But sometimes a few different types of cells may exist together to form a tissue as in the case of a muscle or gland. The same organ may have a few different kinds of tissues as its components.

The three embryological layers of cells differentiate to form all the tissues of the body. The ectoderm gives rise to many of the epithelial tissues and nervous tissue. The mesoderm develops into connective tissue, muscle, bone, blood vessels, organs like the adrenal cortex, kidneys and the lining membranes (mesothelium of the pericardium, pleura, and peritoneum. From the entoderm are derived the lining epithelium of the alimentary canal (other than that of the mouth) of the middle ear and the Eustachian tube, the secretory cells of thyroid and parathyroid, the lining membrane of the larynx and all the passages and the alveoli in the lungs and also of the urinary bladder, urethra and prostate.

The primary tissues (all those that arise from the ectoderm, entoderm and mesoderm collectively) in the body are said to be of four basic kinds—epithelial tissues, connective tissues, contractile tissues and nervous tissue. This nomenclature does not take into account the embryological origin of the tissues but is based more or less on the functions carried out by them.

Epithelial tissues: These have the special function of covering the body as in skin, lining the cavities in the body and also forming alveoli or acini in glands. The transfer of substances from the blood to the lumen of the acini (secretion) of glands or from the lumen of the renal tubule or the alimentary canal to blood (reabsorption or absorption) is a specialised function of some epithelial cells.

Epithelia found in lining and covering membranes will now be described. These consist of cells existing in layers either as one or many. The cells are more or less packed together so that there is very little or no intercellular space. There are also no blood vessels as such, present in these membranes. The cells obtain oxygen and nutriment from blood vessels in the connective tissue on which the lining or covering membrane rests. Epithelial cells are attached to an underlying membrane formed of intercellular substance which provides support for the cells and this non-living membrane is known as the basement membrane. In the case of the thyroid acinar cells however, there is no basement membrane. Constant wear and tear to which epithelium is subjected, especially in the skin and the alimentary canal, necessitates the shedding of damaged cells in large numbers each day and these are replaced by cells derived from the deeper layers of the epithelium where active cell division occurs constantly. Where such loss does not occur, the cells may exist only in a single layer. Wherever the superficial cells of the epithelium are moistened by bodily secretions, as in the cornea and alimentary tract, the cells are in the living state exhibiting their normal activities but those that are not wetted by a fluid dry up and become keratinised – the stratum corneum has cells which have keratin deposited in them and the most superficial ones have lost their viability and are known as epidermal scales. Keratin makes the skin impermeable to water. These superficial cells are lost from the skin in large numbers daily.

Lining or covering epithelial cells are of several kinds, though they are usually brought under two broad categories – simple epithelia and compound epithelia. The simple squamous (pavement) epithelium is formed of a single layer of flat cells, the margins of adjacent cells joined to each other like the pieces of a jig-saw puzzle. The intercellular cementing substance can be stained with silver nitrate which makes it stand out as dark boundaries for the cells. Viewed at from the side, the cells are found to be very thin, with only the nuclear region standing out as slightly thicker than the rest of the cell. The squamous epithelium is capable of transferring substances from one side of it to the other, as in the lung capillaries and the alveoli. The mouth is lined by such epithelium and in this site, the cells

can be easily scraped off for study purposes. It is of interest to mention that the sex chromatin found in cells of females can be demonstrated in the scrapings from the buccal mucosa,

Simple cuboidal epithelium has cells roughly cuboidal in shape, the three dimensions of the cell being more or less equal. This is found in the pigment layer of retina, parts of the labyrinth, germinal epithelium of the ovary, the choroid plexus, ducts and alveoli of many glands and in the acini of the moderately active thyroid gland. These cuboidal cells may get flattened when there is excessive storage of colloid in the thyroid acini. In thyrotoxicosis, they may take the shape of columnar cells.

Simple Columnar Epithelium: Cells have the shape of columns or pillars, i. e. their lengths are much greater than their width or thickness, the cross section being roughly hexagonal. The nuclei are present nearer the base of the cells (away from the free end). These line the glandular acini, especially of the alimentary canal, gall bladder and excretory ducts of certain glands and they secrete mucus (goblet cells also do this). In certain situations, the cells exhibit cilia or minute hair-like processes on the free surface. Such cells which do not secrete mucus may have an absorptive function and for this, microvilli are present on the free surface of these cells. These minute processes are beneath the resolution of the light microscope. Hence, at ordinary magnification, the cell appears to have a brush border. These absorptive cells are found in the intestinal epithelium. The microvilli which are nonmotile are about half a micron in length. These features are also seen in the proximal convoluted tubule in the kidney. The cells contain alkaline phosphatase which may be concerned with sugar absorption. It is likely that the ultrastructures of striated border of intestinal cells and brush border of renal cells may be different from each other.

Compound Epithelial Membranes:—

a) **Stratified Squamous Epithelium:—** In this, there are several layers of cells. The deeper ones are mostly cuboidal and the superficial ones are irregular in shape and flattened. Such an epithelium is found in the epidermis, in the mouth, oesophagus, cornea and other structures.

b) **Stratified Columnar Epithelium** : The deep layers are polyhedral in shape, while the superficial layers contain typical columnar cells. This type of epithelium is seen in the urethra, in the conjunctiva. in the pharynx and in the epiglottis.

c) **Pseudostratified columnar epithelium** : It has the same features as the previously described type except that the stratification is not of a true kind. The nuclei of the cells are at different levels, but the individual cells are arranged in definite layers. Some cells, while standing on the basement membrane, may not extend upto the free surface, while the other cells which are tall are more superficial. This kind is seen in the large ducts of the glands and in the male urethra (cavernous part) and vas deferens.

d) **Pseudostratified Columnar Ciliated Epithelium** : The cells are arranged and exhibit the same features, as in the previous type. The free surface of the cells present cilia. This epithelium is seen in the mucous membrane of the respiratory tract (trachea) in the middle ear and the pharyngotympanic tube (pharyngeal end) and also in the male genital passages like the vas deferens.

Each cilium (under the electron microscope) arises from a small granule-like body in the substance of the cell near the free end (basal corpuscle). In cross section, each cilium shows two central pairs of filaments surrounded by nine pairs of outer ones. The cilia take part in transferring mucus or dust across the surface of the mucous membrane. They execute bending movements which are rapid in one direction and slow in the opposite direction. The former helps to shift materials like mucus and the latter is a movement to restore the initial position of the cilia. Ciliated columnar epithelium is found in the lining of the respiratory tract (the small bronchi and bronchioles), the central canal of the spinal cord (ependyma) and eustachian tube. Ciliary movement is affected by physical and chemical factors. Warmth and calcium salts increase the movements, Cold, carbon dioxide, ether vapour and chloroform depress the movements. It is responsible for the movement of the ovum in the fallopian tube, movements of sperms in the vasa efferentia and shifting of dust

and other particulate material in the respiratory tract. Cilia in the inner ear, by their bending movements, are involved in excitation of the end organs of hearing and equilibration.

e) **Transitional Epithelium:** This term was coined since it was believed that the type referred to was midway between the stratified squamous and the columnar types of epithelium. It is found in the inner lining of the hollow viscera wherein high pressures may build up owing to collection of fluid, as in the urinary bladder. Ordinarily, there are many layers, the basal ones being columnar or cuboidal. The more superficial ones are polyhedral and the cells on the free surface are large and exhibit bulges into the lumen of the viscus. When subjected to stretching, as by distension of the viscus, the superficial layers become flattened into the squamous type, the deeper ones assuming a cuboidal shape. This variety is found in the urinary tract from the renal pelvis down to the urethra.

Certain intracellular details: Each epithelial cell has a single nucleus flattened into a oval disc in the squamous cells, but spherical in most others and even cylindrical in columnar cells. While the epithelial cells present most of the features of all cells in general, certain specialised structures like tonofibrils are seen in the cytoplasm and especially in the stratified squamous cells, they form bundles either straight or wavy in their course.

There is a polarisation in the epithelial cell in that the attached side is different from the free end. It is this polarisation which is seen in the shape of the mitochondria at the base and the top of the cell. The Golgi network is superficial to the nucleus. The basal part of most cells seem to be alike, but the superficial parts are not so. The free surface of the epithelial sheet is covered by a solid material secreted by the cells. This is the cuticle. It may be impregnated with calcium salts. Mucopolysaccharides (chitin) and even the tooth enamel can be considered to be analogous structures. So also the lens capsule in the eye, the tectorial membrane, the reticular laminae and the otolith membrane of the inner ear.

The individual cells in an epithelial sheet are firmly bound to each other, perhaps by intercellular substance. In addition,

certain bridges are seen between neighbouring cells, known as desmosomes which, according to some, may be artifacts of staining procedures. Some intercellular structures known as terminal bars (stainable with iron haematoxylin) are present. They appear as dots in cross section and as short dark lines if they are in the plane of the section.

Epithelial tissues are capable of rapid regeneration by mitosis of deeper cells (see skin).

The term epithelium is generally used for cellular membranes based on the appearance and the functions of the cells which line cavities or cover surfaces in the body. Whatever may be their embryological origin in general, sheets of cells derived from the ectoderm and endoderm of the embryo are generally referred to as epithelium. But the membranes lining the great cavities in the body (peritoneal, pleural and pericardial cavities) are called the mesothelium, though they do not differ from what is specifically called epithelium. They are actually derived from the mesoderm. The inner lining of the blood vessels and lymphatics are called endothelium (derived from the mesoderm). There is one reason for making this hair-splitting distinction. The precursors of endothelial and mesothelial cells, under an appropriate, abnormal or pathological stimulus, can form connective tissue cells but epithelial tissues that arise from ectoderm do not exhibit this kind of metaplasia or abnormal reversion to a more primitive type of tissue; but for this reason there is not much significance in assigning different names to lining membranes in different situations. Rightly, each one should be called epithelium, though conventionally it is not so (for other details see under Skin and Renal tubules).

Exocrine glands have been described as a) simple tubular type (intestinal glands), b) simple coiled tubular (sweat gland), c) simple branched tubular (gastric glands), d) simple branched alveolar (sebaceous glands) and e) compound glands (salivary glands and the mammary glands). The ovary and the testis are considered as cytogenic glands forming the germ cells, the sperm and the ovum. Single cells like the goblet cells, as in large intestine and the respiratory passages, can secrete mucin by themselves.

Compound glands are made up of a number of secreting units, the alveoli or the acini which are lined by secreting cells. The pancreas (exocrine portion) is a good example of such a gland. Several alveoli together form a lobule of the gland with its duct. Several lobules go to form a lobe, its duct arising from the union of lobular ducts. The different lobes jointly form the compound gland with one or two large ducts draining away the secretions from the entire glandular mass. Connective tissue strands or partitions arising from the capsule of the gland give rise to its divisions and subdivisions and they form the stroma of the gland. The active secreting elements are called the parenchyma of the gland.

Secretory epithelial cells : Secretory cells have been divided into apocrine, holocrine and merocrine types. The first of these, concentrates its products of secretion under the free or the luminal surface of the cell. This part of the cell gets, as it were, pinched off from the rest of the cell, to be liberated into the lumen of the gland. Some salivary gland cells are said to be of this type. The holocrine type of cell is itself shed into the glandular lumen, carrying with it, its secretory products. The cells of the sebaceous glands and those of the crypts of Lieberkuhn appear to belong to this variety. The third variety is the merocrine cell which does not undergo any loss of its cell matter during the secretory process. Its secretory material is transferred across its membrane into the hollow spaces of the gland to be carried away by the ducts. Most of the digestive glands have this last variety of cell.

The secretory cell has to synthesise complex substances (high molecular weight) out of relatively simple basic materials (low molecular weight). A secretory cell has, in addition to what other cells have, certain highly developed structures. Recent electron microscopic studies of such cells have advanced our knowledge regarding the intracellular structures like ribosomes (RNA particles) which lie close to the endoplasmic reticulum — 'rough surfaced cisterna' and 'smooth contoured' vesicles and rather well developed Golgi apparatus. The vesicles of the last mentioned structure get packed with the secretory material — enzymes — in the form of zymogen granules which is

the storage form of the enzyme. The digestive enzymes and mucin are seen in the respective secretory cells as zymogen or mucinogen granules, as in the glands of the alimentary canal. The membrane of the zymogen granule may merge or coalesce with the plasma membrane of the secretory cell before the extrusion or the liberation of the enzymes into the lumen of the gland. Even minute canaliculi are seen in some secretory cells like the oxyntic cells in the fundic glands of the stomach. It may be of interest to mention that there are numerous vesicles or ultramicroscopic bag-like structures in the interior of the presynaptic nerve terminals. These structures empty themselves of their contents into the synaptic cleft whenever a nerve impulse travels down a fibre towards the synapse. These vesicles are thought to move nearer the presynaptic membrane before they are depleted of their contents (see Synaptic Transmission).

Connective Tissue : The three kinds of primary tissues—epithelial, nervous and muscular—are held in their proper positions and also the individual cells or groups of cells of these tissues are bound to each other by means of connective tissue which provide so to say, a lattice work or scaffolding. The connective tissue itself gives rise to intercellular substances produced by cellular activity.

The intercellular substances are of two kinds 1) Fibrous 2) Amorphous. The latter itself is further subdivided into ground and cement substances.

The functions of intercellular substances are as follows :

1. To strengthen and support tissues.
2. To act as the vehicle or medium for the transport of nutritive materials to such tissues and cells as are not directly supplied or provided with blood flow and also for the removal of waste products from these isolated tissues and cells.

The fibres in the intercellular substances are collagenic, reticular and elastic. Tendons of muscles are made up of collagenous fibres which in their turn consist of the protein, collagen, of high tensile strength. They can resist mechanical stretching

and hence are very tough. Collagen when boiled gives rise to gelatin and thereby meat of old animals (rich in collagen) is rendered digestible. Leather—processed hides—of animals is rich in collagen. The fibres may be up to 100 microns in width but of great length. They may exist as bundles or individually, depending on the necessity to resist stretch. When treated with alkali and examined under the microscope, they consist of fibrils of less than a micron in diameter. Acids destroy the intra-structure of a collagen fibre. In ordinary histological sections (H & E) collagen fibres appear reddish. When it is necessary to distinguish them from plain muscle, they may be stained with a special stain (Van Geison's microfuscin stain) and they appear red. Mallory's stain also may be used for the same purpose. Collagen fibres are highly refractile when examined under polarised light. Under the electron microscope, the fibrils appear to consist of finer microfibrils or unit fibres which show periodicity of around 600 Å units, analogous to myofibrils. These microfibrils are about 500 Å in diameter. Closer examination under electron microscope shows that the major segments in the microfibrils are made up of still smaller subdivisions. The microfibrils consist of protein filaments of diameter 30 Å.

Reticular fibres form a network, as indicated by their name. They are very delicate and are supported by thicker collagen fibres. They are present under epithelial sheets forming basement membranes. These are not easily seen in H & E sections. They can be impregnated with silver stains, when they appear as fine dark or black lines. Collagen fibres appear light brown with the same technique. The periodic acid schiff (P. A. S.) reaction makes them take on a red color while collagen appears as pale pink. Reticular fibres are not refractile under a polarised light and do not take Van Geison's stain. These show branching but collagen fibres do not. The difference in the staining reaction cannot be explained at present. Some special substances which exist in association with collagen fibrils may make them different from reticular fibres in this respect.

Elastic fibres contain elastin and an albuminoid protein which does not deteriorate with the passage of time. These are highly refractile. The fibres are a micron or so in thickness but of rather

great length. There are no fibrils inside the individual fibres as in the collagen fibres, and as such elastic fibres appear homogenous. Elastin is often present in tissues as complete sheets presenting openings (fenestra) to permit transfer of physiologically important substances. They have no minerals incorporated in them. They are specially stained with Orcein (brown) and other dyes. In physical properties, elastic fibres resemble rubber and they give resilience to the tissues in which they are found.

Amorphous intercellular substances, as mentioned before, are of two kinds—ground and cement substances. They seem to be formed of mucopolysaccharides which are complex molecules having hexosamine and glucuronic acid units combined with protein. These complex compounds are of two types depending upon whether sulphuric acid is present combined with hexosamine in the molecule or not. Hyaluronic acid and chondroitin are non-sulphated types, while chondroitin sulphate is sulphated. Hyaluronic acid is a viscid substance in the polymerised state. It is present in many parts of the body in the intercellular substances and specially in the synovial fluid in the joints. The umbilical cord is a rich source of it. Hyaluronidase, known also as the spreading factor, reduces the viscosity of intercellular substance. The exact physiological significance of this fact is not satisfactorily understood (see fertilization). The sulphated mucopolysaccharides are also broken down by certain specific enzymes. It is very difficult to demonstrate hyaluronic acid histologically as it has not much affinity for stains. Chondroitin sulphuric acid, however, takes on stains, appearing blue or purple. Metachromatic reaction is a property of the ground substances which take on a colour different from that of the stain used. Toluidin blue when used in dilute solutions on ground substances makes them appear reddish violet. The periodic acid schiff reaction has been used in respect of intercellular substances. Aldehydes restore the colour of the basic fuchsin (purple) which has been bleached by sulphurous acid. DNA has this property while RNA does not have it. Reticular fibres are PAS positive. They restore the colour of the dye. Collagen and elastic fibres are only faintly so. Ground substances do not appear to be PAS positive.

Basement membranes are present under epithelial sheets in most situations (thyroid epithelium is an exception to this rule).

Basement membrane which is not easily made out in ordinary histological sections can be revealed by the PAS technique. While some authors consider the basement membrane as made up of solely a compact feltwork of reticular fibres, others believe that it is of a structureless or hyaline material supported by the reticular fibres. The amorphous or hyaline material in the basement membrane may possibly be of the same material as the fibres themselves. Chemically, galactose, fructose, glucose, and mannose may be components of this material and these sugars may be responsible for the positive P.A.S. reaction of the reticular fibres. Reticulin, originally thought to be present in reticular fibres (analogous to the collagen of collagen fibres), may not be a protein. It may be only a substance which responds to the P.A.S. reaction.

Aging and intracellular substances: The process of aging seems to be inseparably connected with the deterioration of intracellular substances. There is also an inability of the connective tissues to produce, in old age, as much of intracellular substances as in young age, especially when there is damage or injury to the tissues. The tissues of the foetus are very rich in these substances and that seems to explain their jelly like character. They also have less of fibrous intracellular substances, but as old age advances, while the fibrous material increases, there is a gradual loss of the ground substance. Also, collagen fibres and bundles increase in quantity. There is deterioration in elastic fibres which become more friable and fragile. They also develop affinity for calcium salts and this fact may underlie the hardening of arteries in old age. The inelastic skin of old people seems to have as its basis, a change for worse in the elastic fibres and not in collagenic fibres. Hormones may have a role in the changes associated with aging.

Extracellular fluid or tissue fluid is dealt with elsewhere. It is now proposed to describe those kinds of connective tissues which have very little intercellular substance and on the contrary, exhibit more of cellular elements. Connective tissue, it is necessary to emphasise, is developed from mesenchyme which in the embryo develops from embryonic mesoderm. Mesenchyme seems to infiltrate into various tissues in the body. Its cells have delicate and long protoplasmic extensions reaching

into the intercellular substance in between other cells. While these extensions may show continuity between one cell and another yet such bridges are not many. These cells have the capacity to differentiate into many kinds of descendent cells. Some of them retain their potentiality to give rise to many kinds of cells under an appropriate stimulus. Thus, the connective tissue cells may be of both undifferentiated and fully differentiated types and they may also give rise to intermediate varieties between the two extremes. A fully differentiated type of connective tissue cell cannot be transformed into any other kind. It is only the relatively undifferentiated cell that retains this potentiality. When required, cells of any type can be produced from primitive ancestral cells which persist in the body throughout life. These cells, in embryonic life, give rise to many types of connective tissues like areolar, adipose, fibrous, cartilagenous, haemopoietic and osseous tissues.

Areolar tissue: This is usually called as loose areolar tissue because it consists of a jelly like amorphous intercellular substance in which some fibres are present. This tissue is highly pliable and can be stretched easily unlike some other kinds of connective tissue (cartilage or bone). This tissue also shows many capillary vascular networks, from which other associated tissues like epithelium derive their oxygen and nutriment. The loose texture of the tissues permit movement. This kind of tissue is not only present under epithelial sheets but also in glandular tissue, between bundles of muscle fibres and around lymph nodes, blood vessels and nerve terminals. When fresh areolar tissue is stretched, bubbles of air appear in it giving it the name areolar tissue. It can be stained in the fresh state as well as in the dry fixed condition. Romanowski stains as are used in haematology, can be used to stain dry areolar tissue preparations. Wet saline preparations can be treated with methylene blue or similar stains. The fibres that are revealed in fresh preparations are of collagenic and elastic type. The former are wavy and show a fibrillar structure. The latter do not show this but appear as dark lines. The ground substance shows metachromasia.

Cellular elements of loose connective tissue:

A) **Stem cells:** These have great potentiality to change into any of the differentiated types. They have no moorings and

are free and are also rounded in shape. Such cells when present in bone marrow are called haemocytoblasts, in the lymph nodes as lymphoblasts and monoblasts.

B) Fibroblasts: They were originally assumed to form fibres of intercellular substance and this view has been accepted by all. These are divided into young and old types, the latter being known as fibrocytes which are more differentiated than the former. The young variety actively produce intercellular substance and have basophilic cytoplasm. The nucleus is somewhat oval and also flattened with an indentation on one side. The nucleus stains lightly and shows fine chromatin granules scattered in it. Some nucleoli may also be seen. Collagen fibres, as has been revealed recently, seem to be formed at the surface of the fibroblast or even farther away. The dentine of teeth appears to be formed in a similar way from the odontoblast which is analogous to the fibroblast in teeth. Collagen itself is considered to arise from a parent substance containing glycine which polymerises to yield collagen. The mode of formation of the ground substance is still to be worked out. But it is possible that the fibroblasts may themselves form the ground substance as well as collagen fibres.

C) Macrophages: (Refer to reticulo-endothelial cells). Foreign body giant cells arise from a fusion of monocytes or macrophages and thus deal with large particles or masses of extraneous material which cannot be phagocytosed by individual micro or macrophages.

D) Mast cells: These are present in large numbers in connective tissue and especially in the areolar tissue. They are stuffed with basophilic granules which form a dense dark mass, most often hiding the centrally placed nucleus. They are P.A.S. positive. Heparin, a substance of large molecular weight and chemically a sulphuric acid ester, has an intimate association with mast cells. The heparin content of a tissue has been found to be dependent on the number of mast cells present in it. Both the mast cell granules and heparin shows metachromatic reaction. It is probable that mast cells produce heparin though this has not been conclusively established. Heparin, it may be recalled, is an anticoagulant and was originally prepared from the liver tissue as its name indicates. Mast cells also contain histamine and

serotonin. Blood vessels have cells similar to the mast cells. Mast cells which are present in the walls of blood vessels may possibly be concerned with prevention of intravascular clotting which, at least on theoretical grounds, may occur in small blood vessels (of narrow diameter) on account of sluggish flow.

E) Plasma cells : Whether these cells belong to the haemopoietic system or to the connective tissue, has not been settled. They are found in haemopoietic tissue and especially the lymph nodes and also in connective tissues. They are concerned with antibody production and hence they occur in sufficient numbers in wet epithelial surfaces which are the portals for absorption and also in the sites of inflammation. They are smaller than mast cells and they are round in shape and have an eccentric nucleus. The so called cart wheel (clock face) arrangement of chromatin flakes in the nucleus is not such a constant feature as is usually taken to be.

F) Fat cells : These are present either singly or in groups. They are a special type of mesenchymal cells devoted to storing of fatty material. In the process of storage, initially, individual droplets of fat appear in the cytoplasm and these latter increase in number and finally amalgamate to form a large globule which pushes the nucleus and the cytoplasm to one side so that the cell takes on a signet ring appearance.

Adipose Tissues : Loose areolar tissue which contains a preponderance of fat cells goes by this name. The fat cells form lobules, each of which is marked off from the other by connective tissue partitions which convey blood vessels. In hibernating animals, the fat droplets in fat cells do not coalesce and this type of fat is known as brown fat.

Dense fibrous tissue formed by fibroblasts has high tensile strength. Tendons and aponeuroses are formed of this tissue. The fibres form sheets or bundles. They may also be disposed in the form of a network. Fibroblasts with flattened nuclei are seen in between different planes of the fibres or different bundles. Dense fibrous tissue is also found in the deep fascia under the skin and in the capsule of viscera.

Synovial fluid may be considered as a special type of liquid ground substance providing lubrication between two surfaces

which move in relation to each other as in joints and also between the inner and outer sheaths of tendons.

CARTILAGE

Cartilage and bone are the two types of somewhat rigid connective tissue. While the latter can resist mechanical strains without showing any bending, cartilage is flexible and yet can retain its shape and resist distortion to an appreciable extent. These two tissues can therefore bear weights within limits. The intracellular substance of cartilage has the consistency of modern plastics and it is in the form of almost solid jelly, chemically made up of mucopolysaccharides (see under intercellular substances elsewhere). The cartilage, as it normally exists in the body, never undergoes calcification (becoming impregnated with calcium salts). But this is what happens to the cartilages in the foetus which are after birth converted into the bones of the skeleton. Membranous ossification of bones in early years of life, is a similar process. There are three types of cartilage described—hyaline, elastic and fibro cartilage.

Hyaline cartilage: Hyaline cartilage, as its name indicates, has a glassy appearance. It is somewhat translucent and of a pearly white tint. It is present in joints as articular cartilage, covering the ends of long bones which form the joint. It can also be seen in the trachea, nose, larynx and the bronchi where it serves to keep the passages patent. It also unites the ribs with the sternum. Microscopically, it is seen that there are cells dispersed either singly or in pairs or even in groups of four, in the intercellular substance. Actually, the cells are lodged in empty spaces or lacunae in the intercellular substance. When more than one cell (chondrocyte) are present, the cell group is termed a cell nest. A lacuna is surrounded by intercellular substance of a slightly different kind. The perilacunar material shows metachromasia with toluidin blue and it is also known as the capsule of the cartilage cell. When more than one cell are present, each lies in its own individual cavity or in a secondary lacuna. A chondrocyte is round in shape, though in stained preparations it presents a shrunken appearance with the cell boundary withdrawn from the walls of

the lacuna. The nucleus is rounded and one or more nucleoli may be present. The cytoplasm of the chondrocytes may show glycogen and fat. When two or more chondrocytes are present together, as in a cell nest, the cells have flat opposing sides, but as these cells grow they become rounded. The intercellular substance consists of both collagen fibres and fibrils and the amorphous type which is a complex of protein and chondroitin sulphuric acid (mucopolysaccharide). This substance is mildly P.A.S. positive. The collagen fibres and fibrils cannot be revealed under the light microscope, since they have the same refractive index as the surrounding matrix. These can be seen under the electron microscope.

Yellow Elastic cartilage : While all the three types of cartilage show elasticity of some degree, this type shows it to the maximum extent owing to the presence of a large number of elastic fibres in its matrix. The external ear (pinna) and the epiglottis, pharyngo-tympanic tube and larynx are structures formed by elastic cartilage which imparts stiffness and simultaneously flexibility, to these parts. The collagen fibres are found even in this kind of cartilage and so also chondroitin sulphate.

White Fibrocartilage : Where high tensile strength is required without the hardness of the bone, fibrocartilage has been found, as in the intervertebral discs, semilunar cartilages of the knee joint and surrounding the edges of the sockets of the hip and shoulder joints and symphysis pubis. The high tensile strength of fibrocartilage is due to abundance of white collagen fibres in it. The chondrocytes are arranged in rows in between the collagen fibre bundles and the intercellular substance is mostly chondroitin sulphuric acid.

Articular cartilage in joints presents cells arranged in layers or zones. The most superficial cells are small and flattened so as to lie parallel to the articular surface. Middle zone has larger cells arranged in columns perpendicular to the articular surface. The deepest layers have large cells with calcified intercellular substance. Collagen fibres are also found in articular cartilage, disposed in coarse bundles.

Perichondrium : Cartilage, except that at the articular surfaces of the joints, is surrounded by a membrane of connective tissue

called perichondrium. Its outer part is made up of fibrous or collagenic connective tissue. In young and growing cartilage, the inner layers of this membrane show cells which can, under appropriate stimuli, become chondroblasts which subsequently get converted to chondrocytes in the fully formed cartilage. As chondroblasts lay down intercellular material, they get separated from each other, getting enclosed in lacunae, thereby coming to be known as chondrocytes.

There is no perichondrium for fibrocartilage which seems to be midway between connective tissue and hyaline cartilage.

Cartilage is devoid of blood vessels. Nutrient and oxygen must diffuse or seep through intercellular substance to reach the chondrocytes. Such of the blood vessels as pass through cartilage (as in epiphyseal plates), are meant to supply other tissues. Outside the perichondrium are present the capillaries which are intended for the nutrition of the cartilage.

BONE

Bone is the most important of the supporting tissues in the body in that it forms the skeletal core of the body and thereby furnishes a rigid support for all the soft tissues of the body. All the bones in the body, in early foetal life, exist in the form of cartilages which later undergo transformation into bones. Bones are usually divided into long bones, as in the limbs and digits; short bones, as in the wrist and ankle; flat bones as in the skull, pelvis, sternum; sesamoid bones which are somewhat flat, irregular and of small dimensions. Those bones which cannot be brought under these categories are called irregular bones. Long bones develop from rods of cartilage, flat bones from membranes and sesamoid bones from tendons. The skeletal bones begin their development before birth, but the formation of the bony skeleton is completed in the middle of the third decade of life.

Bone tissue is of two kinds - compact bone and cancellous bone. The compact bone consists of a number of Haversian systems as seen in cross section under the microscope. A Haversian system consists of the following elements:

a) A central Haversian canal running longitudinally. It holds blood vessels, lymphatics and nerves meant for the bony tissue;

b) Arranged concentrically around the central canal, are a number of thin shells of bone known as the lamellae ;

c) In between the lamellae are spaces, the lacunae, containing lymph and osteocytes (bone cells) ;

d) Connecting the lacunae and the central canal, are a number of minute channels, the canaliculi, carrying lymph containing nourishment. They also lodge numerous fine processes of the osteocytes. The lacunae in general have a radial direction in the Haversian system.

Cancellous bone, having a sponge-like appearance, is made up of a network of Haversian canals covered by lamellae, the whole tissue appearing like a honey-comb. In the interstices of the cancellous bone, red bone marrow is present. Outside the Haversian systems and lying between neighbouring Haversian systems, are small circular plates of bones known as interstitial lamellae. All bones — short, long and irregular — have compact bone outside and cancellous bone inside. In the case of long bones which have each a shaft and two extremities, the shaft has compact bone forming the outer part with a long central canal, the medullary canal. In adults, cancellous tissue in the proximal ends of the long bones contains active or red marrow. The medullary canal in the shaft and the distal end show only inactive or yellow fatty marrow. In the shaft, there is a foramen to allow the entry of the nutrient artery to the bone. The periosteum is a vascular fibrous membrane covering the bones almost completely except over the articular surfaces in the joints which are covered by hyaline cartilage. Periosteum has several functions. It is innervated with nerve fibres and protects the bone from injury by generating pain when injurious stimuli are applied to it. It provides attachment for the tendons of muscles. Blood vessels pass through the periosteum to gain access to the bone tissue proper. In the deeper layers of periosteum, there are cells known as osteoblasts which are responsible for the formation of new bone tissue in the periphery of the bones.

Long bones, as mentioned already, develop from cartilages which appear in foetal life. Bones owe their origin to ossification (deposition of calcium salts) in preexisting connective tissue membranes or cartilage. The former process is known as membranous

ossification and the latter as cartilagenous ossification. The long bones have a primary centre of ossification in the shaft (diaphysis) and a secondary centre of ossification at each end (epiphysis). The increase in girth or thickness as well as the increase in the length of the bone is achieved by cartilagenous ossification. The growth at the ends is brought about by proliferation of epiphyseal cartilage cells leading on to ossification immediately thereafter. These two processes, proliferation and ossification, progress hand in hand, resulting in the lengthening of the bone. The epiphysal cartilage which is responsible for this mechanism disappears when the bone is fully developed as in adulthood. In gigantism resulting from hyperpituitarism, the epiphyseal cartilages are profoundly influenced by growth hormone and this results in excessive lengthwise growth of the bones. In acromegaly, since epiphyseal cartilages have already disappeared before the onset of hyperpituitarism, long bones are not affected – no increase in stature occurs, but bones of the hands and jaw enlarge to give rise to the characteristic symptoms of this condition.

Mention has already been made about osteoblasts which are present in the periosteum of bones which can take on the activity of new bone formation. It must be stressed that bone tissue is not static. Old bone is destroyed and new bone is formed in its place constantly. The preexisting Haversian systems are replaced by new Haversian systems, repeatedly.

Osteoblasts are of mesenchymal origin. They have the ability to secrete or form the specialized intercellular substance of the bone and thereby contribute to the formation of new bone. The freshly formed organic matrix surrounds not only the cell bodies of bone cells (osteoblasts) but also their long processes. Thus, each one of these cells gets isolated from other similar cells and when this process is complete, the cells come to be known as osteocytes. The osteoblast has abundant basophilic cytoplasm and an eccentric nucleus. The golgi apparatus in this cell appears pale (negative Golgi). The staining property of the cytoplasm and the appearance of the Golgi apparatus are suggestive of an active secreting function of the osteoblast. The electron microscope reveals a large number of rough surfaced vesicles of endoplasmic reticulum. The Golgi apparatus reveals many

vesicles. The products of secretion of osteoblasts are collagen and mucopolysaccharides.

Osteoclast : These cells are seen in bone tissue whenever bone resorption takes place. An osteoclast may show single or many nuclei. The cells are large in size and a section may present only a slice of a cell. Osteoclasts may be of different ages. In the young osteoclast, the nucleus is oval and its membrane is smooth, the contained chromatin granules are fine and uniformly spread. There may be one or two nucleoli. Older cells have a wrinkled nuclear membrane and the nuclei are darker stained or even pyknotic (completely dark and small in size). The cytoplasm of a young cell is most often acidophilic with a tinge of basophilism, but the older cell is more acidophilic. Osteoclasts also seem to have a frothy cytoplasm. These cells exhibit what is called as shrinkage spaces, on one side or the other of the cell boundaries and perhaps these are artefacts. On the surface of some of these cells, facing bony tissue, a brush or striated border may be seen. The hair-like processes of these structures appear to extend towards bone and they may be instrumental in effecting resorption of bone. It is now felt that these hair-like processes may really be collagenic and not belong to the cells themselves. Under the electron microscope, very minute villus-like processes are seen with clefts in between. There are also cytoplasmic vesicles which can be made out. Dense material (minerals removed from bone) is also made out. Acid phosphatase and other enzymes are present in the cytoplasm. The mode of action in bone destruction by these cells may be a lowering of the pH of the intercellular fluid which may etch away small pieces of bones, or a precipitation of calcium salts may occur. Regarding the origin of cells, the osteoclast may arise from stem cells covering the bony surfaces (periosteum). It may even happen that the osteoblast, under an appropriate stimulus, can be converted to an osteoclast, since osteoclasts and osteocytes and other cells too have been seen to be incorporated in osteoclasts. Osteoclasts differ from megakaryocytes in that the former has many and separate nuclei, while the latter has a single large continuous nucleus with numerous lobes. Both osteoblasts and osteoclasts function together as indicated before, since bone tissue is constantly being renewed. Osteoclasts appear

to be engaged in removing old bone and osteoblasts in laying down new bone.

The water content (25%) of bone is less than that of any other tissue. The bulk of the weight of the bone is made up by organic material (30%) and inorganic salts (45%). The noncellular material in the bone (matrix) is composed of both organic material and minerals. The organic substances are a protein, ossein and osseomucoid and albuminoid. The minerals are salts of calcium, magnesium and to a less extent, of potassium and sodium. Other elements like phosphorous, iron, chlorine and fluorine are also found in the combined state. Citrate is an important constituent found in the bone. Calcium occurs to the extent of more than 1/6th of the weight of fresh bone and 1/5th of dried bone. Calcium is present in the form of calcium carbonate and tricalcium phosphate. The calcium and phosphorous ratio is about 2.2 : 1. Magnesium is present as Magnesium phosphate $(Mg)_3(PO)_4$. Calcium carbonate and calcium phosphate do not occur as such, but as a complex structure. The name hydroxyapatite $Ca_{10}(OH)_2(PO_4)_6$ is given to this substance, though there is some doubt whether this is the actual substance in the bone. Bones can be decalcified to remove all the inorganic material, for making histological preparations. Ethylene diamine tetra acetic acid (EDTA), at a slightly alkaline pH, has been used for this purpose. A decalcified long bone can be tied into a knot, showing that it has lost its rigidity and hence its weight bearing character.

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